



PMI RESEARCH & DEVELOPMENT

Study ZRHM-REXA-08-US **Clinical Study Report Appendix 16.1.3** **List of IRBs, IRB Approvals, Sample Consent Forms, and** **Written Subject Information**

Study Title: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting

Study Number: ZRHM-REXA-08-US

Product Name: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)

Study Initiated (first subject screened): 17 December 2013

Study Completed (last subject last visit): 12 October 2014

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Sponsor: Philip Morris Products S.A.
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Sponsor Signatories: Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist
Guillaume de La Bourdonnaye, MEng, MSc, Biostatistician
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Ruben Rosoky, MD PhD MFPM, Medical Safety Officer

Version: 1.0

Date: 25 May 2016

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

This document is confidential. Disclosure of any of its contents to third parties is not permitted except by the prior written consent of Philip Morris Products S.A.



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16.1.3 LIST OF IRBS, IRB APPROVALS, SAMPLE CONSENT FORMS, AND WRITTEN SUBJECT INFORMATION

16.1.3.1 IRB INFORMATION

IRB	Investigator	Site Number
MidLands Independent Review Board 8417 Santa Fe Drive, Suite 100, Overland Park, KS 66212	Dr. William Lewis Dr. Frank Farmer	DAL DAY
Chairperson: Kathy Chase, Pharm. D		



16.1.3.2 IRB STUDY SUBMISSION LETTER (ENGLISH)



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999
www.MLIRB.com

INVESTIGATOR REQUEST FOR APPROVAL/FACILITY DESCRIPTION

This form **must** be completed in its entirety and returned to the IRB before your study can be considered for review.
Failure to complete all items may result in delays in your approval.

Please complete a Supplemental Investigator Request for Approval/Facility Description form for EACH additional site where subjects will be seen or as listed on Section 3 of the FDA Form 1572 for this study. This form can be found on our website at www.MLIRB.com.

SPONSOR Philip Morris International PROTOCOL NUMBER ZRHM-REXA-08-US

PRINCIPAL INVESTIGATOR NAME H. Frank Farmer, Jr, MD, PhD, FACP, CPI

A. STUDY INFORMATION**TYPE OF STUDY**

1. ☐ No ☒ Yes Is this study regulated by the FDA? If not, please specify agency: _____
2. ☐ No ☒ Yes Is this a drug study? If no, go to Question No. 3
- ☒ No ☐ Yes Is this study being conducted under an IND?

What was the Date of the IND Submission?

*If yes, please provide one of the following

- ☐ Approval letter from the FDA indicating the IND number
- ☐ Letter from the Sponsor indicating the IND number
- ☐ Sponsor protocol indicating IND number
- ☐ Other (such as IND number indicated in correspondence from Sponsor)

If no, does the study meet the criteria identified in 21 CFR Part 312.2(b)?

- ☐ No ☒ Yes If no, the study must be conducted under an IND.

3. Is this a device study?

☒ No ☐ Yes If no, go to question 4.

- ☐ No ☐ Yes Is this study being conducted under an IDE?

If yes, please provide one of the following

- ☐ IDE Approval letter from the FDA
- ☐ Letter from the Sponsor indicating the IDE approval
- ☐ Copy of Humanitarian Device Exemption (HDE) approval letter from FDA

4. ☒ No ☐ Yes Is this study federally funded?

If yes, please provide the following information

- a. Are you the Grant holder? ☐ No ☐ Yes
- b. Agency(ies) receiving federal funds: _____
- c. Copy of the Grant
- d. The DHHS-approved sample Informed Consent document (if applicable)
- e. The DHHS-approved Protocol (if applicable)



5. Therapeutic Area

- ☐ Allergy/Asthma ☐ Cardiology ☐ CNS (Central Nervous System) ☐ Dermatology
☐ Immunology ☐ Inflammatory/Autoimmune ☐ Neurology ☐ Oncology
☒ Pulmonary ☐ Rheumatology ☐ N/A ☐ Other: _____

6. What is the indication of the study drug or device? smoking _____

7. Is this study? (Please check all the apply)

- ☒ Phase I - normal healthy subjects ☐ Phase I - patients ☐ Phase II
☐ Phase III ☐ Phase IIIb ☐ Phase IV ☐ Nutritional/Food Supplement
☐ Cosmetic ☐ Social Science ☐ Behavioral Science
☐ Other: _____

8. ☒ No ☐ Yes Is this the first time this drug will be given to humans?9. ☒ No ☐ Yes Is this study a medical device study? **If no, go to section B. SITE INFORMATION**
If yes, please provide the following information

- ☐ Statement of Investigator's commitment to the sponsor, per 21 CFR 812.43(a)(4)
☐ Report of prior investigations, if applicable
☐ Device information (for example, directions for use, user's manual, etc.), if applicable

Has the study been determined, by the Sponsor, to be ☐ Significant Risk ☐ Non-Significant Risk
☐ No ☐ Yes If Significant Risk, does the device meet the criteria in Title 21 CFR 812.3(m)?

If no, the device must be submitted as non-significant risk and you must provide a letter from the Sponsor indicating that the device is a non-significant risk and why it was determined to be so.

If yes, identify one of the following you are providing to the IRB

- ☐ Approval letter from the FDA indicating IDE number
☐ Letter from the Sponsor indicating the IDE number
☐ Sponsor protocol indicating IDE number
☐ Other (such as IDE number indicated in correspondence from Sponsor)

- ☐ No ☐ Yes Has the device been cleared/approved for marketing?
☐ No ☐ Yes If yes, is it being used in accordance with its cleared/approved labeling?

B. SITE INFORMATION

FACILITY NAME _Covance CRU, Inc._

ADDRESS _1900 Mason Ave, Suite 140_

CITY _Daytona Beach_

STATE _Florida_

ZIP CODE _32117_

PHONE _386-366-6400_ FAX _386-274-1258_ E-MAIL _heather.camilo@covance.com_

1. ☐ No ☒ Yes Is this the address where all correspondence should be sent?

If no, please list the address where the correspondence should be sent.



2. SETTING OF THE STUDY SITE

- ☐ Single Office Practice ☐ University Research Center ☒ Research Facility
☐ Multi-Office Practice ☐ Hospital ☐ Other _____

3. ☒ No ☐ Yes Has this protocol ever been submitted to another IRB for review?
If yes, please provide explanation on a separate sheet of paper.
4. ☒ No ☐ Yes Does a local IRB have jurisdiction over this site?
If yes, please attach a waiver form from the local IRB delegating responsibility to MLIRB.
The waiver form can be found on our website at www.midlandsirb.com.
5. ☐ No ☒ Yes Is there a specific person assigned to coordinate this study? If yes, please list the name
and title of this person and the telephone number where he/she can be reached.

Name Jasmine Ropers Title Project Manager Phone Number 608-310-8280

6. Estimate the number of personnel to be involved in conducting this study at your site(s), including the Principal Investigator and Sub-Investigators. 62
7. ☐ No ☒ Yes Is there a secure (locked) area for storage of the study drug?
If no, where do you store the drug? _____
8. ☒ No ☐ Yes Are there any community attitudes (religious, ethical, ethnic, or economic) that will affect
the conduct of research at this site? If yes, the attitudes are ☐ Positive ☐ Negative ☐ Neutral
If negative, please attach an explanation on a separate piece of paper.

C. PRINCIPAL INVESTIGATOR INFORMATION

1. ☐ No ☒ Yes Are you currently licensed to practice in the state where this study will be conducted?
State Florida License No. ME 30591 Expiration January 31, 2014
2. ☒ No ☐ Yes Has your license to practice ever been suspended, revoked, or are there any restrictions on
your license? If so, please provide any documentation.
3. How long have you been conducting research? approximately 10 years
4. What training have you had in the protection of human research subjects? (check all that apply)
- | | |
|---|--|
| <input type="checkbox"/> None | <input checked="" type="checkbox"/> Training by the Sponsor (i.e. Investigator meetings) |
| <input type="checkbox"/> OHRP Training Modules | <input checked="" type="checkbox"/> NIH Human Participant Protections Education |
| <input checked="" type="checkbox"/> Certified Investigator Training Initiative (CITI) | <input type="checkbox"/> DIA; Certified Clinical Investigator (CCI) |
| <input type="checkbox"/> ACRP; Certified Clinical Trial Investigator | <input type="checkbox"/> SoCRA; Clinical Research Professional (CRP) |

Please provide a detailed description of the training that study personnel have received in Good Clinical Practice and Human Subject Protection. If you or your study staff have not had appropriate training, courses are provided at no cost to you on the MLIRB website under the "Training" link. The courses are through the Collaborative IRB

Training Initiative Program (CITI) in the Protection of Human Research Subjects. Login using MidLands as the institution. **All relevant staff have completed CITI training modules, NIH Human Subject Protection training, Covance Good Clinical Practice Training (required annually), sponsor-specific GCP training, SOP training regarding the consent process, subject confidentiality, and emergency procedures.**

5. In how many research studies are you currently listed as the Principal Investigator? approximately 10
6. State the number of key staff who will assist in this research study
- | | |
|-----------|--|
| <u>4</u> | Sub-Investigators |
| <u>1</u> | Clinical Research Coordinators |
| <u>3</u> | Pharmacists |
| <u>54</u> | Other (e.g., laboratory specialists, regulatory specialists) |

Please provide a summary of the qualifications for the above-listed study staff. If necessary, attach a separate sheet



Please reference the training listed above. In addition, relevant staff are ACLS and BLS certified, and some staff are certified as CRCC or CCRP. The Principal Investigator is CPI certified. The lab staff is IATA certified, one lab staff member is a Medical Technologist, and one lab staff member is a Clinical Laboratory Technician.

7. ☐ No ☒ Yes Have you or your site(s) been audited by the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP) in the past 5 years?
- If Yes, what were the date(s)? 8/10/2009 _____
- If yes, was a Form FDA 483 or other list of observations issued? ☐ No ☒ Yes
- If yes, please provide a copy of the Form FDA 483 /list of observations and response letter. **Please see attached documentation**
8. ☒ No ☐ Yes Has the FDA ever issued a Warning Letter to you or your study site(s)?
9. ☒ No ☐ Yes Has FDA or OHRP ever terminated any study, or research, your site(s) has participated in, or sanctioned any Principal Investigator, Co-Investigator, or Sub-Investigator at your site?
10. ☒ No ☐ Yes Has any IRB ever withheld or withdrawn your approval as an Investigator?
11. ☒ No ☐ Yes Will a Sub-Investigator be performing study-related procedures that you are not qualified through expertise to perform? If yes, please provide copies of CV(s) and License(s).

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

MASSACHUSETTS INVESTIGATORS ONLY

1. Check here if you are registered with the Massachusetts Department of Public Health to dispense investigational drugs and attach a copy of your current registration.

Research License Number _____ Date of Expiration _____

2. Check here if you are not registered. Please contact the Massachusetts Department of Public Health at (617) 983-6712 for information on obtaining a registration.

Please note that an audit by MLIRB will be performed at your site in accordance with our affiliation agreement with the state of Massachusetts.

D. STATE LAWS

1. ☒ No ☐ Yes Are there any specific state or local regulations/laws governing research in your state? For example, California requires the "California Experimental Bill of Rights." (If you are unsure, please contact your local or state government.)

If yes, please describe _____

2. What is the age of consent in your state for treatment or procedures involved in this research study? 18

3. ☒ No ☐ Yes Does your state or local laws require additional information beyond those required by FDA/OHRP to be in the informed consent (to be legally effective)?

If yes, please explain. Attach additional paperwork, if necessary. _____

E. FINANCIAL DISCLOSURE

During the past year, has any Investigator or Investigators spouse, domestic partner or children, or any person involved in this research study:

1. ☒ No ☐ Yes Been an officer, director, or employee of the sponsor of this research study?
2. ☒ No ☐ Yes Held a significant equity interest in the sponsor of this research study? A significant equity interest would mean any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds \$5,000 aggregated by immediate family member



- during the time the clinical investigator is carrying out the study and for 1 year following completion of the study. Has any arrangement been made where the value of the ownership interests will be affected by the outcome of the research or exceeds 5% interest in any one single entity when aggregated for the immediate family?
3. ☒ No ☐ Yes Had any propriety interest in the research product for this research study a proprietary interest in the product is defined as property or other financial interest including, but not limited to, a patent, trademark, copyright, or licensing agreement?
4. ☒ No ☐ Yes Received, or made any arrangement to receive, any significant payments of other sorts from the sponsor of this research study to support activities of the investigator that have a monetary value of more than \$5,000 aggregated by immediate family member exclusive of the costs of conducting the research study, such as retainers for ongoing consultation or honoraria, during the course of the study?
5. ☒ No ☐ Yes Agreed to, or plan to, accept recruitment bonuses for enrolling subjects into this research study?
6. ☒ No ☐ Yes Entered into any financial arrangement for this research study whereby the value of compensation paid could affect the outcome of this study (compensation affected by the outcome of the study is defined as compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result, or compensation in the form of an equity interest in the sponsor of the study, or in the form of compensation tied to sales of the product, such as royalty interest?)

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

F. EMERGENCY CONTACT INFORMATION AND PROCEDURES

1. In case of an emergency, the Investigator or Sub-Investigator can be reached at the following phone numbers.
- Office Number 386-366-6400
- Mandatory 24-Hour Number 386-366-6400
- Pager Number 386-214-9437
2. Should an emergency occur at your site, how close is the nearest hospital emergency room?
- 2 miles
3. ☒ No ☐ Yes Do you have privileges at the above-mentioned hospital?
- Please list other hospitals where you have privileges and the distance from your facility?
- Hospital Name _____ Distance _____
- Hospital Name _____ Distance _____
4. ☒ No ☐ Yes If you do not have privileges at a hospital, does a Sub-Investigator have privileges?
- Hospital Name _____ Distance _____
- If you or a Sub-Investigator do not have privileges, please attach an SOP for handling emergencies. Please see attached SOP regarding emergency procedures.*
5. What is the response time for a 911 call 3-5 minutes
6. Describe on-site emergency treatment equipment/personnel available for subjects. Please include a listing of the emergency medications on hand. (Use a separate sheet of paper, if necessary.)

EpiPen Auto-Injector (Epinephrine Hydrochloride) Single 0.3 mg dose [0.3 ml], Dey, Adrenalin Chloride Solution (1:1000) (of epinephrine), Monarch or nonproprietary, Aspirin 325 mg, Atropine Sulfate Injection, 1 mg (0.1mg/mL), Hospira or nonproprietary name, Naloxone Hydrochloride Injection, 0.4 mg/mL, Hospira, IMS or nonproprietary name, 2% Lidocaine Hydrochloride Injection, Hospira or nonproprietary name, Diphenhydramine Hydrochloride Capsules, 25 mg, Benedryl Allergy Kapseals or nonproprietary name, 50% Dextrose Injection, Abraxis or nonproprietary name,



Nitroglycerin, Sub Lingual Tablets, 0.4 mg or NitroQuickTM, Ethex or NitrostatTM, Pfizer or NitrotabTM, Able Albuterol Aerosol or Proventil HFA, Schering or Ventolin HFA, GlaxoSmithKline or nonproprietary name, Ammonia Inhalants, Silver Nitrate Applicators, Ativan (Lorazepam) Injection, 2mg/mL or same class (20mg/10mL vial)

(Diphenhydramine (or its equivalent), oxygen, IV Fluids, and epinephrine (or its equivalent) **MUST** be included at sites *where dosing with study drug is performed*.)

G. SUBJECT RECRUITMENT

1. How will subjects be recruited for this study?

☐ Existing Patients ☐ Referrals ☒ Other database

☒ Advertisements (i.e., newspaper, TV, radio, posters, internet, newsletters, brochures, flyers)

2. Will a screening script be utilized for this study?

☐ No ☒ Yes If yes, please submit the screening script for review.

All advertisements and recruitment materials must be reviewed and approved by the IRB prior to use.

PLEASE NOTE THAT THIS IRB DOES NOT APPROVE THE WORDS "FREE," "PAY," "PAID," OR "PAYMENT" IN ANY RECRUITMENT MATERIAL.

H. SUBJECT INFORMATION

1. Subjects for this study will be recruited from the following groups.

☐ Gender ☒ Male ☒ Female
☐ Ethnic Backgrounds ☒ Caucasian ☒ African-American ☒ Asian-American
☒ Native-American ☒ Hispanic ☒ Other as determined by subject
☐ Economic Status ☒ Upper Income ☒ Middle Income ☒ Lower Income

I. VULNERABLE POPULATIONS

1. Identify any vulnerable populations that are included in the study design, per the protocol:

☐ Children – include page number in protocol where identified _____
☐ Students (participating in research sponsored by the college/university they currently attend) – include page number in protocol where identified _____
☐ Economically disadvantaged – include page number in protocol where identified _____
☐ Educationally disadvantaged – include page number in protocol where identified _____
☐ Illiterate – include page number in protocol where identified _____
☐ Persons with limited capacity to consent – include page number in protocol where identified _____
☐ Terminally ill – include page number in protocol where identified _____
☐ Employees of the Principal Investigator/sponsor – include page number in protocol where identified _____
☒ None
☐ Other (describe) _____ include page number in protocol where identified _____

2. ☐ No ☐ Yes If any vulnerable populations are identified above, are the safeguards to protect these participants identified in the protocol? If yes, include page numbers where identified _____



If enrolling vulnerable populations into the study please describe in detail, on a separate page, the additional safeguards you will use to protect the rights and welfare of these subjects.

J. INFORMED CONSENT

1. Describe the Informed Consent process at this site by answering the following questions. Also, if you have an SOP, please attach. **Covance consent SOP is on file.**
 - a. Will the consent discussion with the potential subject take place in a private area at your site?
☐ No ☒ Yes If no, please attach a written explanation.
 - b. Identify all individuals at your site authorized to conduct the consent discussion with potential subjects.
☒ PI ☒ Sub I ☒ Research Coordinator ☒ Study Nurse ☒ Other trained staff _____
 - c. Identify the education on conducting a consent discussion that has been provided to the individuals identified above.
☒ In-house Education ☐ Role Play ☒ Education provided by a professional association
☒ Education provided by Sponsor/CRO ☒ Job Orientation ☒ Other SOP training _____
 - d. How long will the potential subject be allowed to review the Informed Consent document?
☒ As long as needed ☐ Overnight
☐ During the study visit ☐ Other _____
 - e. Will the PI or Sub-Investigator be available to answer subject questions during the consent process?
☐ No ☒ Yes If no, please attach a written explanation.
2. ☒ No ☐ Yes Do you anticipate enrolling any non-English speaking subjects?
If yes, what language? _____. Please note, the Informed Consent will need to be translated into this language.
3. ☐ No ☐ Yes Do you have someone who is fluent in the language of the non-English speaking subjects you plan to enroll? If no, how do you plan to provide Informed Consent to this person?

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

4. ☐ No ☒ Yes Will the subjects be compensated for their participation in this study?
If yes, please state specifically what the compensation will be. For example, what will the subject receive for each visit and the total amount they will receive if they complete the entire study. If necessary, attach a separate sheet of paper.

Please see attached draft ICF for compensation breakdown _____

5. With regard to the research-related injury section of the Informed Consent, is there an Investigator's Agreement or Contract with the Sponsor that outlines the provisions in place to pay for medical care should a subject become injured? ☐ No ☒ Yes If yes, please provide that verbiage for Board's review. If no, please ensure that verbiage provided in your Informed Consent is adequate. ***Please see consent SOP on file, and the language in the ICF is adequate and has been approved by their study sponsor.***

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

Please provide a description of the consent process including:

1. Who will be conducting the consent discussion? screening staff _____
2. Who will provide consent or permission: ☒ subject ☐ LAR ☐ parent ☐ other: _____



3. What steps are taken to minimize the possibility of coercion or undue influence? please see consent SOP on file

4. Will there be any situations in which consent will be obtained from a Legally Authorized Representative (LAR) rather than the participant? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the participant to their participation in the procedures involved in this study.

If you are unsure of the answer to this question, it is recommended that you obtain legal advice.

5. If your site will be enrolling children, will there be any situations in which a legal guardian can provide permission for the child's participation? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the child to general medical care. *If you are unsure of the answer to this question, it is recommended that you obtain legal advice.*

In order to for the IRB to determine whether the regulatory criteria pertaining to the consent process are met, please check the following that apply for your site.

- ☒ The investigator will obtain the legally effective consent of the participant or the participant's legally authorized representative.
- ☒ The circumstances of the consent process provide the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate.
- ☒ The circumstances of the consent process minimize the possibility of coercion or undue influence.
- ☒ The individuals communicating information to the participant or the legally authorized representative during the consent process provide that information in language understandable to the participant or the representative.
- ☒ The information to be communicated to the participant or the representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative is made to waive or appear to waive any of the participant's legal rights.
- ☒ The information to be communicated to the participant or the legally authorized representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative releases or appears to release the investigator, the sponsor, MLIRB, or its agents from liability for negligence.
- ☒ The subject, or the subject's legally authorized representative, will sign and date the consent form and receive a signed and dated copy of the consent form to keep
- ☐ Will you be utilizing a short form consent document? ☒ No ☐ Yes If no, move onto section "K".
If yes, the following regulatory criteria must be met.

- ☐ The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative.
- ☐ A written summary embodies the basic and appropriate additional elements of disclosure.
- ☐ There will be a witness to the oral presentation.
- ☐ For participants who do not speak English, the witness will be conversant in both English and the language of the participant.
- ☐ The participant or the participant's legally authorized representative will sign the consent document.
- ☐ If the research is FDA-regulated, the participant or the participant's legally authorized representative will sign and date the consent document.
- ☐ The witness will sign both the short form and a copy of the summary.
- ☐ The person actually obtaining consent will sign a copy of the summary.
- ☐ A copy of the short form will be given to the participant or the participant's legally authorized representative.



☐ A copy of the summary will be given to the participant or the participant's legally authorized representative.

K. MONITORING PLAN

MLIRB requires adequate provisions for monitoring the data to ensure the safety and protection of study participants.

A. Identify your monitoring plan.

☐ Data and Safety Monitoring Board (DSMB)

☒ Is the plan detailed in the protocol? ☐ No ☒ Yes

If yes, include page number in protocol where identified. **Section 10.1**

If no, please provide this information as an attachment.

☐ Other (describe in detail)

☐ None (provide rationale)

L. MANAGEMENT OF INFORMATION

Describe the plan for management of information that is relevant to the protection of the participants, such as reporting of: (Use a separate sheet of paper, if necessary.)

1. Unanticipated problems involving risks to participants or others **Unanticipated problems will be reported to the IRB if the PI deems them reportable. Sites will be required to assess why the issue occurred and come up with a plan to ensure it does not happen again.**

2. Interim Results **Interim Results are not required for this study.**

3. Protocol Modifications **Protocol amendments and letters of administrative change will be submitted to the IRB for review and approval. Sites will be trained an applicable changes.**

M. BILLING INFORMATION

The party responsible for payment of MLIRB fees for this study at your site is

Site or Company name Covance CRU, Inc. Attention Heather Camilo

Address 1900 Mason Ave, Suite 140

Phone 386-366-6405 FAX 386-274-1258 Email heather.camilo@covance.com

N. SECURITY AND CONFIDENTIALITY

What precautions will be used to maintain the confidentiality and security of study records at your site? **(Please check all that apply.)**

☒ Paper-base records will be kept in a secure location and will be accessible only to personnel involved in this study.

☒ Computer-based files will be available only to personnel involved in this study through the use of access privileges and passwords.

☒ Prior to accessing any study-related information, site personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information.

☒ Whenever feasible, identifiers will be removed from study-related information.

☐ Other, please specify. _____

**U. PRIVACY**

Privacy refers to persons and people have an interest in controlling access to themselves, including the time they give the information, the place they given information, the nature of the information being given, and the nature of the research experience.

Please describe provisions to protect the privacy interests of study participants.

- ☐ No ☒ Yes Will the study participants be consented in a private area away from the public?
- ☐ No ☒ Yes Will study-related assessments be conducted in a private area?
- ☐ No ☒ Yes Will the private information collected be limited to what is required in the research study?
- ☐ No ☒ Yes Are there any additional provisions in place for protecting the privacy of the study participants?
- ☐ No ☐ Yes If "No" was answered to any of the above, please provide an explanation on a separate sheet of paper.

P. PRINCIPAL INVESTIGATOR STATEMENT AND SIGNATURE

As Principal Investigator, I agree

- that all of the information reported in this document is correct and I will not make any changes in the conduct of the research without prior approval from MLIRB;
- to abide by all of my responsibilities as outlined in the federal regulations and all applicable state and local laws;
- to report all changes in research activities and unanticipated problems involving risk to human subjects or others;
- to ensure that the privacy of study participants is protected;
- to ensure procedures are in place to maintain the confidentiality of the research data;
- to promptly report to MLIRB findings that could affect the safety of the study participants, influence the conduct of the study, or alter MLIRB approval to continue the study;
- to report safety information to MidLands which may help to provide additional protections for study participant's safety and well-being. Such reports include, but are not limited to, summaries from data safety monitoring groups (e.g., data monitoring committee, data and safety monitoring board, or data and safety monitoring committee; and
- to communicate to study participants any information that may directly affect participant safety, medical care, or willingness to continue participation.

I have read the MLIRB "Guidelines for Investigators" and agree to operate in compliance with MLIRB procedures set forth.

I understand that MLIRB, or one of its representatives, reserves the right to visit this study site at any time, with or without appropriate notice.


Principal Investigator Signature

27 JUN 2013
Date

H. Frank Farmer Jr.
Principal Investigator Printed Name



8417 Santa Fe, Suite 100, Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999
www.MLIRB.com

INVESTIGATOR REQUEST FOR APPROVAL/FACILITY DESCRIPTION

This form **must** be completed in its entirety and returned to the IRB before your study can be considered for review.
Failure to complete all items may result in delays in your approval.

Please complete a Supplemental Investigator Request for Approval/Facility Description form for **EACH additional site where subjects will be seen or as listed on Section 3 of the FDA Form 1572 for this study.** This form can be found on our website at www.MLIRB.com.

SPONSOR Philip Morris Products S.A. PROTOCOL NUMBER ZRHM-REXA-08-US
PRINCIPAL INVESTIGATOR NAME William Lewis, MD.

A. STUDY INFORMATION**TYPE OF STUDY**

1. ☐ No ☒ Yes Is this study regulated by the FDA? If not, please specify agency: _____
2. ☐ No ☒ Yes Is this a drug study? If no, go to Question No. 3
- ☒ No ☐ Yes Is this study being conducted under an IND?

What was the Date of the IND Submission?

*If yes, please provide one of the following

- ☐ Approval letter from the FDA indicating the IND number
- ☐ Letter from the Sponsor indicating the IND number
- ☐ Sponsor protocol indicating IND number
- ☐ Other (such as IND number indicated in correspondence from Sponsor)

If no, does the study meet the criteria identified in 21 CFR Part 312.2(b)?

- ☐ No ☒ Yes If no, the study must be conducted under an IND.

3. Is this a device study?

- ☒ No ☐ Yes If no, go to question 4.
- ☐ No ☐ Yes Is this study being conducted under an IDE?

If yes, please provide one of the following

- ☐ IDE Approval letter from the FDA
- ☐ Letter from the Sponsor indicating the IDE approval
- ☐ Copy of Humanitarian Device Exemption (HDE) approval letter from FDA

4. ☒ No ☐ Yes Is this study federally funded?

If yes, please provide the following information

- a. Are you the Grant holder? ☐ No ☐ Yes
- b. Agency(ies) receiving federal funds: _____
- c. Copy of the Grant
- d. The DHHS-approved sample Informed Consent document (if applicable)
- e. The DHHS-approved Protocol (if applicable)



5. Therapeutic Area

- ☐ Allergy/Asthma ☐ Cardiology ☐ CNS (Central Nervous System) ☐ Dermatology
☐ Immunology ☐ Inflammatory/Autoimmune ☐ Neurology ☐ Oncology
☒ Pulmonary ☐ Rheumatology ☐ N/A ☐ Other: _____

6. What is the indication of the study drug or device?

Smoking

7. Is this study? (Please check all the apply)

- ☒ Phase I - normal healthy subjects ☐ Phase I – patients ☐ Phase II
☐ Phase III ☐ Phase IIIb ☐ Phase IV ☐ Nutritional/Food Supplement
☐ Cosmetic ☐ Social Science ☐ Behavioral Science
☐ Other: _____

8. ☒ No ☐ Yes Is this the first time this drug will be given to humans?9. ☒ No ☐ Yes Is this study a medical device study? **If no, go to section B. SITE INFORMATION**
If yes, please provide the following information

- ☐ Statement of Investigator's commitment to the sponsor, per 21 CFR 812.43(a)(4)
☐ Report of prior investigations, if applicable
☐ Device information (for example, directions for use, user's manual, etc.), if applicable

Has the study been determined, by the Sponsor, to be ☒ Significant Risk ☐ Non-Significant Risk
☐ No ☒ Yes If Significant Risk, does the device meet the criteria in Title 21 CFR 812.3(m)?

If no, the device must be submitted as non-significant risk and you must provide a letter from the Sponsor indicating that the device is a non-significant risk and why it was determined to be so.

If yes, identify one of the following you are providing to the IRB

- ☐ Approval letter from the FDA indicating IDE number
☐ Letter from the Sponsor indicating the IDE number
☐ Sponsor protocol indicating IDE number
☐ Other (such as IDE number indicated in correspondence from Sponsor)

- ☐ No ☐ Yes Has the device been cleared/approved for marketing?
☐ No ☐ Yes If yes, is it being used in accordance with its cleared/approved labeling?

B. SITE INFORMATION

FACILITY NAME Covance Clinical Research Unit, Inc.
ADDRESS 1341 W. Mockingbird Lane Ste. 300E and 400E
CITY Dallas STATE TX ZIP CODE 75247

1. ☐ No ☒ Yes Is this the address where all correspondence should be sent?
If no, please list the address where the correspondence should be sent.



2. SETTING OF THE STUDY SITE

- ☐ Single Office Practice ☐ University Research Center ☒ Research Facility
☐ Multi-Office Practice ☐ Hospital ☐ Other _____

3. ☒ No ☐ Yes Has this protocol ever been submitted to another IRB for review?
If yes, please provide explanation on a separate sheet of paper.
4. ☒ No ☐ Yes Does a local IRB have jurisdiction over this site?
If yes, please attach a waiver form from the local IRB delegating responsibility to MLIRB.
The waiver form can be found on our website at www.midlandsirb.com.
5. ☐ No ☒ Yes Is there a specific person assigned to coordinate this study? If yes, please list the name
and title of this person and the telephone number where he/she can be reached.

Name Jasmine Ropers Title Project Manager Phone Number 608-310-8280

6. Estimate the number of personnel to be involved in conducting this study at your site(s), including the Principal Investigator and Sub-Investigators. 60
7. ☐ No ☒ Yes Is there a secure (locked) area for storage of the study drug?
If no, where do you store the drug? _____
8. ☒ No ☐ Yes Are there any community attitudes (religious, ethical, ethnic, or economic) that will affect
the conduct of research at this site? If yes, the attitudes are ☒ Positive ☐ Negative ☐ Neutral
If negative, please attach an explanation on a separate piece of paper.

C. PRINCIPAL INVESTIGATOR INFORMATION

1. ☐ No ☒ Yes Are you currently licensed to practice in the state where this study will be conducted?
State TX License No. F4212 Expiration 28Feb2014
2. ☐ No ☐ Yes Has your license to practice ever been suspended, revoked, or are there any restrictions on
your license? If so, please provide any documentation.
3. How long have you been conducting research? 6 years
4. What training have you had in the protection of human research subjects? (check all that apply)
- ☐ None ☒ Training by the Sponsor (i.e. Investigator meetings)
☐ OHRP Training Modules ☒ NIH Human Participant Protections Education
☒ Certified Investigator Training Initiative (CITI) ☐ DIA; Certified Clinical Investigator (CCI)
☐ ACRP; Certified Clinical Trial Investigator ☐ SoCRA; Clinical Research Professional (CRP)

Please provide a detailed description of the training that study personnel have received in Good Clinical Practice and Human Subject Protection. If you or your study staff have not had appropriate training, courses are provided at no cost to you on the MLIRB website under the "Training" link. The courses are through the Collaborative IRB

Training Initiative Program (CITI) in the Protection of Human Research Subjects. Login using MidLands as the institution.

5. In how many research studies are you currently listed as the Principal Investigator? Approximately 10
6. State the number of key staff who will assist in this research study
- | | |
|-----------|--|
| <u>2</u> | Sub-Investigators |
| <u>2</u> | Clinical Research Coordinators |
| <u>3</u> | Pharmacists |
| <u>48</u> | Other (e.g., laboratory specialists, regulatory specialists) |

Please provide a summary of the qualifications for the above-listed study staff. If necessary, attach a separate sheet



7. ☐ No ☒ Yes Have you or your site(s) been audited by the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP) in the past 5 years?
If Yes, what were the date(s)? 28Feb2011, 11Apr2011
If yes, was a Form FDA 483 or other list of observations issued? ☐ No ☒ Yes
If yes, please provide a copy of the Form FDA 483 /list of observations and response letter. **Previously Provided to MLIRB**
8. ☒ No ☐ Yes Has the FDA ever issued a Warning Letter to you or your study site(s)?
9. ☒ No ☐ Yes Has FDA or OHRP ever terminated any study, or research, your site(s) has participated in, or sanctioned any Principal Investigator, Co-Investigator, or Sub-Investigator at your site?
10. ☒ No ☐ Yes Has any IRB ever withheld or withdrawn your approval as an Investigator?
11. ☒ No ☐ Yes Will a Sub-Investigator be performing study-related procedures that you are not qualified through expertise to perform? If yes, please provide copies of CV(s) and License(s).

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

MASSACHUSETTS INVESTIGATORS ONLY

1. Check here if you are registered with the Massachusetts Department of Public Health to dispense investigational drugs and attach a copy of your current registration.

Research License Number _____ Date of Expiration _____

2. Check here if you are not registered. Please contact the Massachusetts Department of Public Health at (617) 983-6712 for information on obtaining a registration.

Please note that an audit by MLIRB will be performed at your site in accordance with our affiliation agreement with the state of Massachusetts.

D. STATE LAWS

1. ☒ No ☐ Yes Are there any specific state or local regulations/laws governing research in your state?
For example, California requires the "California Experimental Bill of Rights." (If you are unsure, please contact your local or state government.)
If yes, please describe _____

2. What is the age of consent in your state for treatment or procedures involved in this research study? 18

3. ☒ No ☐ Yes Does your state or local laws require additional information beyond those required by FDA/OHRP to be in the informed consent (to be legally effective)?

If yes, please explain. Attach additional paperwork, if necessary. _____

E. FINANCIAL DISCLOSURE

During the past year, has any Investigator or Investigators spouse, domestic partner or children, or any person involved in this research study:

1. ☒ No ☐ Yes Been an officer, director, or employee of the sponsor of this research study?
2. ☒ No ☐ Yes Held a significant equity interest in the sponsor of this research study? A significant equity interest would mean any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds \$5,000 aggregated by immediate family member during the time the clinical investigator is carrying out the study and for 1 year following completion of the study. Has any arrangement been made where the value of the ownership interests will be affected by the outcome of the research or exceeds 5% interest in any one single entity when aggregated for the immediate family?
3. ☒ No ☐ Yes Had any propriety interest in the research product for this research study a proprietary interest in the product is defined as property or other financial interest including, but not limited to, a patent, trademark, copyright, or licensing agreement?



4. ☒ No ☐ Yes Received, or made any arrangement to receive, any significant payments of other sorts from the sponsor of this research study to support activities of the investigator that have a monetary value of more than \$5,000 aggregated by immediate family member exclusive of the costs of conducting the research study, such as retainers for ongoing consultation or honoraria, during the course of the study?
5. ☒ No ☐ Yes Agreed to, or plan to, accept recruitment bonuses for enrolling subjects into this research study?
6. ☒ No ☐ Yes Entered into any financial arrangement for this research study whereby the value of compensation paid could affect the outcome of this study (compensation affected by the outcome of the study is defined as compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result, or compensation in the form of an equity interest in the sponsor of the study, or in the form of compensation tied to sales of the product, such as royalty interest?)

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

F. EMERGENCY CONTACT INFORMATION AND PROCEDURES

1. In case of an emergency, the Investigator or Sub-Investigator can be reached at the following phone numbers.

Office Number 214-647-9300

Mandatory 24-Hour Number 972-955-5373

Pager Number _____

2. Should an emergency occur at your site, how close is the nearest hospital emergency room?

2 miles

3. ☒ No ☐ Yes Do you have privileges at the above-mentioned hospital?

Please list other hospitals where you have privileges and the distance from your facility?

Hospital Name _____ Distance _____

Hospital Name _____ Distance _____

4. ☒ No ☐ Yes If you do not have privileges at a hospital, does a Sub-Investigator have privileges?

Hospital Name _____ Distance _____

If you or a Sub-Investigator do not have privileges, please attach an SOP for handling emergencies.

5. What is the response time for a 911 call under 5 minutes (average 4:16)

6. Describe on-site emergency treatment equipment/personnel available for subjects. Please include a listing of the emergency medications on hand. (Use a separate sheet of paper, if necessary.)

ACLS Certified personnel, AED, EpiPen Auto Injector (Adult) Single 0.3mg dose (0.3ml), Epinephrine 1:1000 (1mg/ml), Aspirin 325mg tablets, Atropine Sulfate INJ 1mg (0.1mg/ml), Naloxone HCl INJ 0.4mg/ml, Lidocaine HCl INJ 2%, Diphenhydramine HCL 25mg capsules, Diphenhydramine HCL INJ 50mg/ml vial, Dextrose INJ 50%, Nitroglycerine Sub Lingual Tablets 0.4mg tablets, Albuterol Aerosol (albuterol sulfate) 200 metered inhalations, Ammonia Inhalants, Silver Nitrate Applicators, Diazepam INJ 5mg/ml, Epinephrine INJ, 1:10,000 1mg (0.1mg/ml), EpiPen Jr. Auto Injector, Single 0.15mg dose (0.15ml), Glucagon INJ 1mg/unit, SoluMedrol INJ 125mg/2ml, oxygen

(Diphenhydramine (or its equivalent), oxygen, IV Fluids, and epinephrine (or its equivalent) **MUST** be included at sites *where dosing with study drug is performed*.)

G. SUBJECT RECRUITMENT

1. How will subjects be recruited for this study?

☒ Existing Patients ☐ Referrals ☐ Other _____



X Advertisements (i.e., newspaper, TV, radio, posters, internet, newsletters, brochures, flyers)

2. Will a screening script be utilized for this study?

☐ No ☒ Yes If yes, please submit the screening script for review.

All advertisements and recruitment materials must be reviewed and approved by the IRB prior to use.

PLEASE NOTE THAT THIS IRB DOES NOT APPROVE THE WORDS "FREE," "PAY," "PAID," OR "PAYMENT" IN ANY RECRUITMENT MATERIAL.

H. SUBJECT INFORMATION

1. Subjects for this study will be recruited from the following groups.

- | | | | |
|--|---------------------------------------|---|---|
| <input checked="" type="checkbox"/> Gender | <input type="checkbox"/> Male | <input type="checkbox"/> Female | |
| <input checked="" type="checkbox"/> Ethnic Backgrounds | <input type="checkbox"/> Caucasian | <input type="checkbox"/> African-American | <input type="checkbox"/> Asian-American |
| <input type="checkbox"/> Native-American | <input type="checkbox"/> Hispanic | <input type="checkbox"/> Other _____ | |
| <input type="checkbox"/> Economic Status | <input type="checkbox"/> Upper Income | <input type="checkbox"/> Middle Income | <input type="checkbox"/> Lower Income |

I. VULNERABLE POPULATIONS

1. Identify any vulnerable populations that are included in the study design, per the protocol:

- ☐ Children – include page number in protocol where identified _____
- ☐ Students (participating in research sponsored by the college/university they currently attend) – include page number in protocol where identified _____
- ☐ Economically disadvantaged – include page number in protocol where identified _____
- ☐ Educationally disadvantaged – include page number in protocol where identified _____
- ☐ Illiterate – include page number in protocol where identified _____
- ☐ Persons with limited capacity to consent – include page number in protocol where identified _____
- ☐ Terminally ill – include page number in protocol where identified _____
- ☐ Employees of the Principal Investigator/sponsor – include page number in protocol where identified _____
- ☒ None
- ☐ Other (describe) _____ include page number in protocol where identified _____

2. ☐ No ☐ Yes If any vulnerable populations are identified above, are the safeguards to protect these participants identified in the protocol? If yes, include page numbers where identified _____

If enrolling vulnerable populations into the study please describe in detail, on a separate page, the additional safeguards you will use to protect the rights and welfare of these subjects.

J. INFORMED CONSENT

1. Describe the Informed Consent process at this site by answering the following questions. Also, if you have an SOP, please attach.

- a. Will the consent discussion with the potential subject take place in a private area at your site?
☐ No ☒ Yes If no, please attach a written explanation.
- b. Identify all individuals at your site authorized to conduct the consent discussion with potential subjects.
☒ PI ☒ Sub I ☒ Research Coordinator ☒ Study Nurse ☒ Other Screening Coordinator
- c. Identify the education on conducting a consent discussion that has been provided to the individuals identified above.



- ☒ In-house Education ☐ Role Play ☐ Education provided by a professional association
☐ Education provided by Sponsor/CRO ☐ Job Orientation ☒ Other ICF Training

d. How long will the potential subject be allowed to review the Informed Consent document?

- ☒ As long as needed ☐ Overnight
☐ During the study visit ☐ Other _____

e. Will the PI or Sub-Investigator be available to answer subject questions during the consent process?

- ☐ No ☒ Yes If no, please attach a written explanation.

2. ☐ No ☒ Yes Do you anticipate enrolling any non-English speaking subjects?

If yes, what language? Spanish Please note, the Informed Consent will need to be translated into this language.

3. ☐ No ☒ Yes Do you have someone who is fluent in the language of the non-English speaking subjects you plan to enroll? If no, how do you plan to provide Informed Consent to this person?

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

4. ☐ No ☒ Yes Will the subjects be compensated for their participation in this study?

If yes, please state specifically what the compensation will be. For example, what will the subject receive for each visit and the total amount they will receive if they complete the entire study. If necessary, attach a separate sheet of paper. **Please see attached ICF for compensation breakdown**

5. With regard to the research-related injury section of the Informed Consent, is there an Investigator's Agreement or Contract with the Sponsor that outlines the provisions in place to pay for medical care should a subject become injured? ☐ No ☒ Yes If yes, please provide that verbiage for Board's review. If no, please ensure that verbiage provided in your Informed Consent is adequate.

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

Please provide a description of the consent process including:

1. Who will be conducting the consent discussion? Screening Coordinator, Clinical Research Coordinator, or assigned trained staff

2. Who will provide consent or permission: ☒ subject ☐ LAR ☐ parent ☐ other: _____

3. What steps are taken to minimize the possibility of coercion or undue influence? Appropriate staff training

4. Will there be any situations in which consent will be obtained from a Legally Authorized Representative (LAR) rather than the participant? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the participant to their participation in the procedures involved in this study.

If you are unsure of the answer to this question, it is recommended that you obtain legal advice.

5. If your site will be enrolling children, will there be any situations in which a legal guardian can provide permission for the child's participation? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the child to general medical care. *If you are unsure of the answer to this question, it is recommended that you obtain legal advice.*



In order for the IRB to determine whether the regulatory criteria pertaining to the consent process are met, please check the following that apply for your site.

- ☒ The investigator will obtain the legally effective consent of the participant or the participant's legally authorized representative.
- ☒ The circumstances of the consent process provide the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate.
- ☒ The circumstances of the consent process minimize the possibility of coercion or undue influence.
- ☒ The individuals communicating information to the participant or the legally authorized representative during the consent process provide that information in language understandable to the participant or the representative.
- ☒ The information to be communicated to the participant or the representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative is made to waive or appear to waive any of the participant's legal rights.
- ☒ The information to be communicated to the participant or the legally authorized representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative releases or appears to release the investigator, the sponsor, MLIRB, or its agents from liability for negligence.
- ☒ The subject, or the subject's legally authorized representative, will sign and date the consent form and receive a signed and dated copy of the consent form to keep.
- ☐ Will you be utilizing a short form consent document? ☒ No ☐ Yes If no, move onto section "K".
If yes, the following regulatory criteria must be met.

- ☐ The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative.
- ☐ A written summary embodies the basic and appropriate additional elements of disclosure.
- ☐ There will be a witness to the oral presentation.
- ☐ For participants who do not speak English, the witness will be conversant in both English and the language of the participant.
- ☐ The participant or the participant's legally authorized representative will sign the consent document.
- ☐ If the research is FDA-regulated, the participant or the participant's legally authorized representative will sign and date the consent document.
- ☐ The witness will sign both the short form and a copy of the summary.
- ☐ The person actually obtaining consent will sign a copy of the summary.
- ☐ A copy of the short form will be given to the participant or the participant's legally authorized representative.
- ☐ A copy of the summary will be given to the participant or the participant's legally authorized representative.

K. MONITORING PLAN

MLIRB requires adequate provisions for monitoring the data to ensure the safety and protection of study participants.

A. Identify your monitoring plan.

- ☐ Data and Safety Monitoring Board (DSMB)

☒ Is the plan detailed in the protocol? ☐ No ☒ Yes

If yes, include page number in protocol where identified. Section 10.1

If no, please provide this information as an attachment.

- ☐ Other (describe in detail)
- ☐ None (provide rationale)

L. MANAGEMENT OF INFORMATION

Describe the plan for management of information that is relevant to the protection of the participants, such as reporting of: (Use a separate sheet of paper, if necessary.)



1. Unanticipated problems involving risks to participants or others Will follow MidLands IRB requirements
2. Interim Results Will follow MidLands IRB requirements
3. Protocol Modifications Will follow MidLands IRB requirements

M. BILLING INFORMATION

The party responsible for payment of MLIRB fees for this study at your site is

Site or Company name Covance Clinical Research Unit, Inc. Attention Shannon Perez

Address 1341 W. Mockingbird Lane, Ste. 400E, Dallas, TX 75247

Phone 214-647-3949 FAX 214-920-9057 Email shannon.perez@covance.com

N. SECURITY AND CONFIDENTIALITY

What precautions will be used to maintain the confidentiality and security of study records at your site? **(Please check all that apply.)**

- ☒ Paper-base records will be kept in a secure location and will be accessible only to personnel involved in this study.
- ☒ Computer-based files will be available only to personnel involved in this study through the use of access privileges and passwords.
- ☒ Prior to accessing any study-related information, site personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information.
- ☒ Whenever feasible, identifiers will be removed from study-related information.
- ☐ Other, please specify. _____

O. PRIVACY

Privacy refers to persons and people have an interest in controlling access to themselves, including the time they give the information, the place they given information, the nature of the information being given, and the nature of the research experience.

Please describe provisions to protect the privacy interests of study participants.

- ☐ No ☒ Yes Will the study participants be consented in a private area away from the public?
- ☐ No ☒ Yes Will study-related assessments be conducted in a private area?
- ☐ No ☒ Yes Will the private information collected be limited to what is required in the research study?
- ☐ No ☒ Yes Are there any additional provisions in place for protecting the privacy of the study participants?
- ☐ No ☐ Yes If "No" was answered to any of the above, please provide an explanation on a separate sheet of paper.

P. PRINCIPAL INVESTIGATOR STATEMENT AND SIGNATURE

As Principal Investigator, I agree



- that all of the information reported in this document is correct and I will not make any changes in the conduct of the research without prior approval from MLIRB;
- to abide by all of my responsibilities as outlined in the federal regulations and all applicable state and local laws;
- to report all changes in research activities and unanticipated problems involving risk to human subjects or others;
- to ensure that the privacy of study participants is protected;
- to ensure procedures are in place to maintain the confidentiality of the research data;
- to promptly report to MLIRB findings that could affect the safety of the study participants, influence the conduct of the study, or alter MLIRB approval to continue the study;
- to report safety information to MidLands which may help to provide additional protections for study participant's safety and well-being. Such reports include, but are not limited to, summaries from data safety monitoring groups (e.g., data monitoring committee, data and safety monitoring board, or data and safety monitoring committee; and
- to communicate to study participants any information that may directly affect participant safety, medical care, or willingness to continue participation.

I have read the MLIRB "Guidelines for Investigators" and agree to operate in compliance with MLIRB procedures set forth.

I understand that MLIRB, or one of its representatives, reserves the right to visit this study site at any time, with or without appropriate notice.

①

W L

Principal Investigator Signature

02 Jun 2013

Date

William Lewis, MD

Principal Investigator Printed Name

① Duplicate signature. Please Refer to page 10 of 10 dated 28 JUN 2013.
HE11amay2016



- that all of the information reported in this document is correct and I will not make any changes in the conduct of the research without prior approval from MLIRB;
- to abide by all of my responsibilities as outlined in the federal regulations and all applicable state and local laws;
- to report all changes in research activities and unanticipated problems involving risk to human subjects or others;
- to ensure that the privacy of study participants is protected;
- to ensure procedures are in place to maintain the confidentiality of the research data;
- to promptly report to MLIRB findings that could affect the safety of the study participants, influence the conduct of the study, or after MLIRB approval to continue the study;
- to report safety information to Midlands which may help to provide additional protections for study participant's safety and well-being. Such reports include, but are not limited to, summaries from data safety monitoring groups (e.g., data monitoring committee, data and safety monitoring board, or data and safety monitoring committee; and
- to communicate to study participants any information that may directly affect participant safety, medical care, or willingness to continue participation.

I have read the MLIRB "Guidelines for Investigators" and agree to operate in compliance with MLIRB procedures set forth.

I understand that MLIRB, or one of its representatives, reserves the right to visit this study site at any time, with or without appropriate notice.

William Lewis
Principal Investigator Signature

28 Jan 2013
Date

William Lewis, MD
Principal Investigator Printed Name



16.1.3.3 IRB STUDY SUBMISSION LETTER (LOCAL LANGUAGE)

Not applicable.



16.1.3.4 IRB STUDY APPROVAL LETTER (ENGLISH)



July 2, 2013

William Lewis, M.D.
Covance Clinical Research Unit, Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Dear Dr. Lewis:

The MidLands Independent Review Board (MLIRB) met on this date and reviewed the Clinical Study Protocol ZRHM-REXA-08-US, Version number: Final 1.0, Revision date: 26 June 2013, entitled "A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting." A quorum was present. A copy of the IRB membership list is enclosed.

The IRB approved the Clinical Study Protocol without modification.

The IRB reviewed the THS 2.2 Menthol Investigator's Brochure, Version number: Version 1.0, Edition number: Edition 1, Release date: 11 April 2013, as well as the User Manual for Tobacco Heating Device (Model 2.2) ©2013.

The IRB reviewed your credentials and site(s) information and approved you to conduct the study as Principal Investigator at the site(s) indicated below:

Covance Clinical Research Unit, Inc.
1341 W. Mockingbird Lane, Suite 400E & 300E
Dallas, TX 75247

The IRB reviewed and approved the "Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with modifications and determined that the Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent guidelines (21 CFR Part 50) and ICH Guidelines. Copies of the "Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with revisions shown are enclosed.

Copies of the revised approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1, dated 07/02/13), "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1, dated 07/02/13) and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1, dated 07/02/13) stamped by the MLIRB are also enclosed.



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 2

The Board reviewed and approved the following documents without modification:

- "Product Use Questionnaire"
- "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011)
- "Cough Assessment" with Translation Certifications (English into United States Spanish) as well as (English in to United States English)
- "Fagerstrom Test for Nicotine Dependence" with Translation Certifications (English into United States Spanish) as well as (English in to United States English)
- "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" (English)
- "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" with Translation Certifications (English into United States Spanish)
- "Prochaska 'Stage of Change' Questionnaire"
- "Modifier Cigarette Evaluation Questionnaire (mCEQ)" (English)
- "Modifier Cigarette Evaluation Questionnaire (mCEQ)" with Translation Certifications (English into United States Spanish)
- HST Questionnaire" (Version 2.0 18/APR/2013)

Copies of the above approved documents stamped by MLIRB are enclosed.

The IRB must review and approve the produced video/audio prior to broadcast. Please submit to the IRB as soon as possible.

Continuing review of this clinical trial must take place at intervals appropriate to the degree of risk. The IRB has determined that you must submit a report on the progress of this study annually from your approval date. Continuing approval of the clinical trial is contingent upon receipt of the report by this IRB.

This study is approved and you may commence (start) the research.

APPROVAL DATE: JULY 2, 2013

EXPIRATION DATE: JULY 1, 2014

In addition to submitting an annual report, your responsibilities as Principal Investigator are indicated in the attached MLIRB "Guidelines for Investigator." Please read this document. These guideline can also be found on our website at www.mlirb.com.

The aforementioned approvals are conditional upon the completion of any pre-investigational requirements by the U.S. Food and Drug Administration.

MLIRB operates in compliance with federal regulations governing Independent Review Boards set forth in 21 CFR Part 56 and regulations governing Informed Consent set forth in 21 CFR Part 50, and the Department of Health and Human Services 45 CFR Part 46. MLIRB is also in compliance with ICH Guidelines for Good Clinical Practice.



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 3

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1) stamped by MLIRB
"Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1) stamped by MLIRB
Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1) stamped by MLIRB
"Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with revisions shown
Approved "Product Use Questionnaire" stamped by MLIRB
Approved "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011) stamped by MLIRB
Approved "Cough Assessment" (English) stamped by MLIRB
Approved "Cough Assessment" (Spanish) stamped by MLIRB
Approved "Fagerstrom Test for Nicotine Dependence" (English) stamped by MLIRB
Approved "Fagerstrom Test for Nicotine Dependence" (Spanish) stamped by MLIRB
Approved "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" (English) stamped by MLIRB
Approved "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" (Spanish) stamped by MLIRB
Approved "Prochaska 'Stage of Change' Questionnaire" stamped by MLIRB
Approved "Modifier Cigarette Evaluation Questionnaire (mCEQ)" (English) stamped by MLIRB
Approved "Modifier Cigarette Evaluation Questionnaire (mCEQ)" (Spanish)
Approved HST Questionnaire" (Version 2.0 18/APR/2013) stamped by MLIRB
User Manual for Tobacco Heating Device (Model 2.2) ©2013 stamped by MLIRB
MLIRB Membership List
MLIRB "Guidelines for Investigators"

cc: Celisa Tolan, Covance Clinical Research Unit, w/enclosures



July 2, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Dear Dr. Farmer:

The MidLands Independent Review Board (MLIRB) met on this date and reviewed the Clinical Study Protocol ZRHM-REXA-08-US, Version number: Final 1.0, Revision date: 26 June 2013, entitled "A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting." A quorum was present. A copy of the IRB membership list is enclosed.

The IRB approved the Clinical Study Protocol without modification.

The IRB reviewed the THS 2.2 Menthol Investigator's Brochure, Version number: Version 1.0, Edition number: Edition 1, Release date: 11 April 2013, as well as the User Manual for Tobacco Heating Device (Model 2.2) ©2013.

The IRB reviewed your credentials and site(s) information and approved you to conduct the study as Principal Investigator at the site(s) indicated below:

Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

The IRB reviewed and approved the "Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with modifications and determined that the Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent guidelines (21 CFR Part 50) and ICH Guidelines. Copies of the "Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with revisions shown are enclosed.

Copies of the revised approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1, dated 07/02/13), "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1, dated 07/02/13) and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1, dated 07/02/13) stamped by the MLIRB are also enclosed.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 2

The Board reviewed and approved the following documents without modification:

- "CoRA Script" (V3)
- "Subject Calendar Cohort 1" (Version 1, 26Jun2013)
- Advertisements (Print ad, :30 Radio ad, Abbreviated online ad, Online ad, and Abbreviated Ads – Outdoor)
- "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)"
- "Prochaska 'Stage of Change' Questionnaire"
- "Product Use Questionnaire"
- "SES Questionnaire"
- "Questionnaire on smoking urges (QSU)"
- "Meta-questionnaire"
- "Smoking Questionnaire"
- "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011)
- "Modifier Cigarette Evaluation Questionnaire (mCEQ)"
- HST Questionnaire" (Version 2.0 18/APR/2013)
- "Cough Assessment" with Translation Certification (English into United States English)
- "Fagerstrom Test for Nicotine Dependence" with Translation Certification (English into United States English)

Copies of the above approved documents stamped by MLIRB are enclosed.

The IRB must review and approve the produced video/audio prior to broadcast. Please submit to the IRB as soon as possible.

Continuing review of this clinical trial must take place at intervals appropriate to the degree of risk. The IRB has determined that you must submit a report on the progress of this study annually from your approval date. Continuing approval of the clinical trial is contingent upon receipt of the report by this IRB.

This study is approved and you may commence (start) the research.

APPROVAL DATE: JULY 2, 2013

EXPIRATION DATE: JULY 1, 2014

In addition to submitting an annual report, your responsibilities as Principal Investigator are indicated in the attached MLIRB "Guidelines for Investigator." Please read this document. These guideline can also be found on our website at www.mlirb.com.

The aforementioned approvals are conditional upon the completion of any pre-investigational requirements by the U.S. Food and Drug Administration.

MLIRB operates in compliance with federal regulations governing Independent Review Boards set forth in 21 CFR Part 56 and regulations governing Informed Consent set forth in 21 CFR Part 50, and the Department of Health and Human Services 45 CFR Part 46. MLIRB is also in compliance with ICH Guidelines for Good Clinical Practice.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 3

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1) stamped by MLIRB
"Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1) stamped by MLIRB
Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1) stamped by MLIRB
"Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with revisions shown
Approved "CoRA Script" (V3) stamped by MLIRB
Approved "Subject Calendar Cohort 1" (Version 1, 26Jun2013) stamped by MLIRB
Approved Advertisements (Print ad, :30 Radio ad, Abbreviated online ad, Online ad, and Abbreviated Ads – Outdoor) stamped by MLIRB
Approved "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" stamped by MLIRB
Approved "Prochaska 'Stage of Change' Questionnaire" stamped by MLIRB
Approved "Product Use Questionnaire" stamped by MLIRB
Approved "SES Questionnaire" stamped by MLIRB
Approved "Questionnaire on smoking urges (QSU)" stamped by MLIRB
Approved "Meta-questionnaire" stamped by MLIRB
Approved "Smoking Questionnaire" stamped by MLIRB
Approved "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011) stamped by MLIRB
Approved "Modifier Cigarette Evaluation Questionnaire (mCEQ)" stamped by MLIRB
Approved HST Questionnaire" (Version 2.0 18/APR/2013) stamped by MLIRB
Approved "Cough Assessment" stamped by MLIRB
Approved "Fagerstrom Test for Nicotine Dependence" stamped by MLIRB
User Manual for Tobacco Heating Device (Model 2.2) ©2013 stamped by MLIRB
MLIRB Membership List
MLIRB "Guidelines for Investigators"

cc: Heather Camilo, Covance CRU Inc., w/enclosures



16.1.3.5 IRB STUDY APPROVAL LETTER (LOCAL LANGUAGE)

Not applicable.



16.1.3.6 IRB PROTOCOL AMENDMENTS SUBMISSION LETTERS (ENGLISH)



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview	
Protocol #	ZHRM-REXA-08-US
Date of this request	20 Nov 2013
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI
Fax	386-274-1258
Email	Heather.camilo@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting
Sponsor	PMI
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial
Proposed study period	to
Current IRB approval period	2013 to 2014
Primary contact person	Daytona Beach- Heather Camilo, Dallas- Celisa Tolan
Change(s)	
Brief description of changes being made	Protocol amendment, revised IB, revised ICF, questionnaires
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input checked="" type="checkbox"/> Investigator's Brochure <input checked="" type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input checked="" type="checkbox"/> Other (specify): questionnaires, draft revised ICF
Check all that apply	<input type="checkbox"/> This change does not increase risks to participants enrolled in the study <input checked="" type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain</i>



why the change is necessary (for example, the change is proposed by the sponsor):
All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
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APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	13 Dec 2013
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI		
Fax	386-274-1258	Email	Heather.camilo@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	PMI		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	2013 to 2014
Primary contact person	Daytona Beach- Heather Camilo, Dallas- Celisa Tolan		

Change(s)

Brief description of changes being made	Protocol amendment, revised ICF, protocol signature pages
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input type="checkbox"/> This change does not increase risks to participants enrolled in the study <input checked="" type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain</i>



why the change is necessary (for example, the change is proposed by the sponsor):
All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



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APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	14 Jan 2014
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI		
Fax	386-274-1258	Email	Heather.camilo@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	PMI		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	2013 to 2014
Primary contact person	Daytona Beach- Heather Camilo		

Change(s)

Brief description of changes being made	Protocol amendment, revised ICF, revised ads, revised scripts
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input checked="" type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>



All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	14 Jan 2014
Principal Investigator Name and Site Address	William Lewis, MD		
Fax	214-920-9057	Email	celisa.tolan@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	Phillip Morris		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	02Jul2013 to 01Jul2014
Primary contact person	Celisa Tolan – Regulatory Specialist		

Change(s)

Brief description of changes being made	Protocol amendment, revised ICF, revised ads, revised scripts
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input checked="" type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>



All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview			
Protocol #	ZHRM-REXA-08-US	Date of this request	14April2014
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI		
Fax	386-274-1258	Email	Regina.oegerle@Covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	Phillip Morris		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	17Dec2013 to 12June2014	Current IRB approval period	02-July-2013 to 01-July-2014
Primary contact person	Regina Oegerle		
Change(s)			
Brief description of changes being made	Revised Main ICF, Biobanking ICF, PGx ICF, Protocol Amendment, Protocol Amendment Signature Page		
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form(Main, PGx and Biobanking ICF) <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):		
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input checked="" type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>		



Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	14Apr2014
Principal Investigator Name and Site Address	William Lewis, MD		
Fax	214-920-9057	Email	celisa.tolan@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	Phillip Morris		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	02Jul2013 to 01Jul2014
Primary contact person	Celisa Tolan – Regulatory Specialist		

Change(s)

Brief description of changes being made	Protocol amendment V5, revised Main ICF, Biobanking ICF and PGx ICF
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input checked="" type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):



All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



16.1.3.7 IRB PROTOCOL AMENDMENTS SUBMISSION LETTERS (LOCAL LANGUAGE)

Not applicable.



16.1.3.8 IRB PROTOCOL AMENDMENTS APPROVAL LETTERS (ENGLISH)



November 26, 2013

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis:

The MidLands Independent Review Board (MLIRB) met on this date to review the revised THS.2.2 Menthol Investigator's Brochure, Version number: Final 1.0, Edition number: Edition 2, Release date: 14 November 2013, the revised Clinical Study Protocol, Version number: Final 2.0, Revision date: 19 November 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ)," Smoking questionnaire (SQ)) for the above-referenced study.

The IRB approved revised Clinical Study Protocol, Version number: Final 2.0, Revision date: 19 November 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation" as well as the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ)," and "Smoking questionnaire (SQ)") without modification and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 2, dated 11/26/13) as well the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ)," and "Smoking questionnaire (SQ)") stamped by the MLIRB are enclosed.



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
November 26, 2013
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Kathy Chase'.

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation"
(Version 2) stamped by MLIRB
Approved revised "Behavioral Risk Factor Surveillance System Questionnaire 2011" stamped
by MLIRB
Approved revised "Human Smoking Topography Questionnaire" stamped by MLIRB
Approved revised "Prochaska 'Stage of Change' Questionnaire" stamped by MLIRB
Approved revised "SES Questionnaire" stamped by MLIRB
Approved revised "Meta-questionnaire (to be answered after SQ)" stamped by MLIRB
Approved revised "Smoking questionnaire (SQ)" stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures



November 26, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

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H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No. ZRHM-REXA-08-US
November 26, 2013
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December 13, 2013

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, as well as the revised "Informed Consent Authorization to Participate in a Clinical Investigation" for the above-referenced study.

I approved revised Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, without modification and the revised "Informed Consent Authorization to Participate in a Clinical Investigation" with modifications and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines. A copy of the "Informed Consent Authorization to Participate in a Clinical Investigation" with revision shown is enclosed.

A copy of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 3, dated 12/13/13) stamped by the MLIRB is also enclosed.

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 3) stamped by MLIRB

"Informed Consent Authorization to Participate in a Clinical Investigation" with revisions shown

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosures



December 13, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

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Sponsor: Philip Morris Products S.A.

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I approved revised Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, as well as the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" without modification and the revised "Informed Consent Authorization to Participate in a Clinical Investigation" with modifications and determined that the revised Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines. A copy of the "Informed Consent Authorization to Participate in a Clinical Investigation" with revisions shown is enclosed.

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Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

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"Informed Consent Authorization to Participate in a Clinical Investigation" with revisions shown
Approved revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 2) stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures

8417 Santa Fe Drive Suite 100 Overland Park, KS 66212

Toll free: 800 636 4445 Phone: 913 385 1414 Fax: 913 385 9999 www.MLIRB.com



January 14, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the revised Clinical Study Protocol, Version number: Final 4.0, Revision date: 14 January 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) for the above-referenced study.

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William Lewis, M.D.
Protocol No.: ZRHM-REXA-08-US
January 14, 2014
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

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Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

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January 14, 2014

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Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 5, dated 1/14/14) as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) stamped by the MLIRB are enclosed.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No.: ZRHM-REXA-08-US
January 14, 2014
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in blue ink that reads 'Lynsey Hartman'.

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

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cc: Heather Camilo, Covance CRU Inc., w/enclosures



April 14, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2" Amendment N°2 Version: Final 5.0, Date 14 April 2014, the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" for the above-referenced study.

I approved the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2" Amendment N°2 Version: Final 5.0, Date 14 April 2014, the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" without modification and determined that the revised Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 31.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 5, dated 04/14/14), the "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples" (Version 2, dated 04/14/14) as well as the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 2, dated 04/14/14) stamped by MLIRB are enclosed.

William Lewis, M.D.
Protocol No.: ZRHM-REXA-08-US
April 14, 2014
Page 2

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Sincerely,

Lyman Hartsman

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D., Chairperson

KC/lh

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H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No.: ZRHM-REXA-08-US
April 14, 2014
Page 2

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Sincerely,

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Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D., Chairperson

KC/lh

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cc: Heather Camilo, Covance CRU Inc., w/enclosures



16.1.3.9 IRB PROTOCOL AMENDMENTS APPROVAL LETTERS (LOCAL LANGUAGE)

Not applicable.



16.1.3.10 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 001 SUBMISSION LETTER (ENGLISH)



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999
www.MLIRB.com

INVESTIGATOR REQUEST FOR APPROVAL/FACILITY DESCRIPTION

This form **must** be completed in its entirety and returned to the IRB before your study can be considered for review.
Failure to complete all items may result in delays in your approval.

*Please complete a Supplemental Investigator Request for Approval/Facility Description form **for EACH additional site where subjects will be seen** or as listed on Section 3 of the FDA Form 1572 for this study. This form can be found on our website at www.MLIRB.com.*

SPONSOR Philip Morris International PROTOCOL NUMBER ZRHM-REXA-08-US

PRINCIPAL INVESTIGATOR NAME H. Frank Farmer, Jr, MD, PhD, FACP, CPI

A. STUDY INFORMATION**TYPE OF STUDY**

1. ☐ No ☒ Yes Is this study regulated by the FDA? If not, please specify agency: _____
2. ☐ No ☒ Yes Is this a drug study? If no, go to Question No. 3
- ☒ No ☐ Yes Is this study being conducted under an IND?

What was the Date of the IND Submission?

*If yes, please provide one of the following

- ☐ Approval letter from the FDA indicating the IND number
- ☐ Letter from the Sponsor indicating the IND number
- ☐ Sponsor protocol indicating IND number
- ☐ Other (such as IND number indicated in correspondence from Sponsor)

If no, does the study meet the criteria identified in 21 CFR Part 312.2(b)?

- ☐ No ☒ Yes If no, the study must be conducted under an IND.

3. Is this a device study?

☒ No ☐ Yes If no, go to question 4.

- ☐ No ☐ Yes Is this study being conducted under an IDE?

If yes, please provide one of the following

- ☐ IDE Approval letter from the FDA
- ☐ Letter from the Sponsor indicating the IDE approval
- ☐ Copy of Humanitarian Device Exemption (HDE) approval letter from FDA

4. ☒ No ☐ Yes Is this study federally funded?

If yes, please provide the following information

- a. Are you the Grant holder? ☐ No ☐ Yes
- b. Agency(ies) receiving federal funds: _____
- c. Copy of the Grant
- d. The DHHS-approved sample Informed Consent document (if applicable)
- e. The DHHS-approved Protocol (if applicable)



5. Therapeutic Area

- ☐ Allergy/Asthma ☐ Cardiology ☐ CNS (Central Nervous System) ☐ Dermatology
☐ Immunology ☐ Inflammatory/Autoimmune ☐ Neurology ☐ Oncology
☒ Pulmonary ☐ Rheumatology ☐ N/A ☐ Other: _____

6. What is the indication of the study drug or device? smoking _____

7. Is this study? (Please check all the apply)

- ☒ Phase I - normal healthy subjects ☐ Phase I - patients ☐ Phase II
☐ Phase III ☐ Phase IIIb ☐ Phase IV ☐ Nutritional/Food Supplement
☐ Cosmetic ☐ Social Science ☐ Behavioral Science
☐ Other: _____

8. ☒ No ☐ Yes Is this the first time this drug will be given to humans?9. ☒ No ☐ Yes Is this study a medical device study? **If no, go to section B. SITE INFORMATION**

If yes, please provide the following information

- ☐ Statement of Investigator's commitment to the sponsor, per 21 CFR 812.43(a)(4)
☐ Report of prior investigations, if applicable
☐ Device information (for example, directions for use, user's manual, etc.), if applicable

Has the study been determined, by the Sponsor, to be ☐ Significant Risk ☐ Non-Significant Risk
☐ No ☐ Yes If Significant Risk, does the device meet the criteria in Title 21 CFR 812.3(m)?

If no, the device must be submitted as non-significant risk and you must provide a letter from the Sponsor indicating that the device is a non-significant risk and why it was determined to be so.

If yes, identify one of the following you are providing to the IRB

- ☐ Approval letter from the FDA indicating IDE number
☐ Letter from the Sponsor indicating the IDE number
☐ Sponsor protocol indicating IDE number
☐ Other (such as IDE number indicated in correspondence from Sponsor)

- ☐ No ☐ Yes Has the device been cleared/approved for marketing?
☐ No ☐ Yes If yes, is it being used in accordance with its cleared/approved labeling?

B. SITE INFORMATION

FACILITY NAME _Covance CRU, Inc._

ADDRESS _1900 Mason Ave, Suite 140_

CITY _Daytona Beach_

STATE _Florida_

ZIP CODE _32117_

PHONE _386-366-6400_ FAX _386-274-1258_ E-MAIL _heather.camilo@covance.com_

1. ☐ No ☒ Yes Is this the address where all correspondence should be sent?

If no, please list the address where the correspondence should be sent.



2. SETTING OF THE STUDY SITE

- ☐ Single Office Practice ☐ University Research Center ☒ Research Facility
☐ Multi-Office Practice ☐ Hospital ☐ Other _____

3. ☒ No ☐ Yes Has this protocol ever been submitted to another IRB for review?
If yes, please provide explanation on a separate sheet of paper.
4. ☒ No ☐ Yes Does a local IRB have jurisdiction over this site?
If yes, please attach a waiver form from the local IRB delegating responsibility to MLIRB.
The waiver form can be found on our website at www.midlandsirb.com.
5. ☐ No ☒ Yes Is there a specific person assigned to coordinate this study? If yes, please list the name
and title of this person and the telephone number where he/she can be reached.

Name Jasmine Ropers Title Project Manager Phone Number 608-310-8280

6. Estimate the number of personnel to be involved in conducting this study at your site(s), including the Principal Investigator and Sub-Investigators. 62
7. ☐ No ☒ Yes Is there a secure (locked) area for storage of the study drug?
If no, where do you store the drug? _____
8. ☒ No ☐ Yes Are there any community attitudes (religious, ethical, ethnic, or economic) that will affect
the conduct of research at this site? If yes, the attitudes are ☐ Positive ☐ Negative ☐ Neutral
If negative, please attach an explanation on a separate piece of paper.

C. PRINCIPAL INVESTIGATOR INFORMATION

1. ☐ No ☒ Yes Are you currently licensed to practice in the state where this study will be conducted?
State Florida License No. ME 30591 Expiration January 31, 2014
2. ☒ No ☐ Yes Has your license to practice ever been suspended, revoked, or are there any restrictions on
your license? If so, please provide any documentation.
3. How long have you been conducting research? approximately 10 years
4. What training have you had in the protection of human research subjects? (check all that apply)
☐ None ☒ Training by the Sponsor (i.e. Investigator meetings)
☐ OHRP Training Modules ☒ NIH Human Participant Protections Education
☒ Certified Investigator Training Initiative (CITI) ☐ DIA; Certified Clinical Investigator (CCI)
☐ ACRP; Certified Clinical Trial Investigator ☐ SoCRA; Clinical Research Professional (CRP)

Please provide a detailed description of the training that study personnel have received in Good Clinical Practice and Human Subject Protection. If you or your study staff have not had appropriate training, courses are provided at no cost to you on the MLIRB website under the "Training" link. The courses are through the Collaborative IRB

Training Initiative Program (CITI) in the Protection of Human Research Subjects. Login using MidLands as the institution. **All relevant staff have completed CITI training modules, NIH Human Subject Protection training, Covance Good Clinical Practice Training (required annually), sponsor-specific GCP training, SOP training regarding the consent process, subject confidentiality, and emergency procedures.**

5. In how many research studies are you currently listed as the Principal Investigator? approximately 10
6. State the number of key staff who will assist in this research study
4 Sub-Investigators
1 Clinical Research Coordinators
3 Pharmacists
54 Other (e.g., laboratory specialists, regulatory specialists)

Please provide a summary of the qualifications for the above-listed study staff. If necessary, attach a separate sheet



Please reference the training listed above. In addition, relevant staff are ACLS and BLS certified, and some staff are certified as CRCC or CCRP. The Principal Investigator is CPI certified. The lab staff is IATA certified, one lab staff member is a Medical Technologist, and one lab staff member is a Clinical Laboratory Technician.

7. ☐ No ☒ Yes Have you or your site(s) been audited by the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP) in the past 5 years?
- If Yes, what were the date(s)? 8/10/2009 _____
- If yes, was a Form FDA 483 or other list of observations issued? ☐ No ☒ Yes
- If yes, please provide a copy of the Form FDA 483 /list of observations and response letter. **Please see attached documentation**
8. ☒ No ☐ Yes Has the FDA ever issued a Warning Letter to you or your study site(s)?
9. ☒ No ☐ Yes Has FDA or OHRP ever terminated any study, or research, your site(s) has participated in, or sanctioned any Principal Investigator, Co-Investigator, or Sub-Investigator at your site?
10. ☒ No ☐ Yes Has any IRB ever withheld or withdrawn your approval as an Investigator?
11. ☒ No ☐ Yes Will a Sub-Investigator be performing study-related procedures that you are not qualified through expertise to perform? If yes, please provide copies of CV(s) and License(s).

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

MASSACHUSETTS INVESTIGATORS ONLY

1. Check here if you are registered with the Massachusetts Department of Public Health to dispense investigational drugs and attach a copy of your current registration.

Research License Number _____ Date of Expiration _____

2. Check here if you are not registered. Please contact the Massachusetts Department of Public Health at (617) 983-6712 for information on obtaining a registration.

Please note that an audit by MLIRB will be performed at your site in accordance with our affiliation agreement with the state of Massachusetts.

D. STATE LAWS

1. ☒ No ☐ Yes Are there any specific state or local regulations/laws governing research in your state? For example, California requires the "California Experimental Bill of Rights." (If you are unsure, please contact your local or state government.)

If yes, please describe _____

2. What is the age of consent in your state for treatment or procedures involved in this research study? 18

3. ☒ No ☐ Yes Does your state or local laws require additional information beyond those required by FDA/OHRP to be in the informed consent (to be legally effective)?

If yes, please explain. Attach additional paperwork, if necessary. _____

E. FINANCIAL DISCLOSURE

During the past year, has any Investigator or Investigators spouse, domestic partner or children, or any person involved in this research study:

1. ☒ No ☐ Yes Been an officer, director, or employee of the sponsor of this research study?
2. ☒ No ☐ Yes Held a significant equity interest in the sponsor of this research study? A significant equity interest would mean any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds \$5,000 aggregated by immediate family member



- during the time the clinical investigator is carrying out the study and for 1 year following completion of the study. Has any arrangement been made where the value of the ownership interests will be affected by the outcome of the research or exceeds 5% interest in any one single entity when aggregated for the immediate family?
3. ☒ No ☐ Yes Had any propriety interest in the research product for this research study a proprietary interest in the product is defined as property or other financial interest including, but not limited to, a patent, trademark, copyright, or licensing agreement?
4. ☒ No ☐ Yes Received, or made any arrangement to receive, any significant payments of other sorts from the sponsor of this research study to support activities of the investigator that have a monetary value of more than \$5,000 aggregated by immediate family member exclusive of the costs of conducting the research study, such as retainers for ongoing consultation or honoraria, during the course of the study?
5. ☒ No ☐ Yes Agreed to, or plan to, accept recruitment bonuses for enrolling subjects into this research study?
6. ☒ No ☐ Yes Entered into any financial arrangement for this research study whereby the value of compensation paid could affect the outcome of this study (compensation affected by the outcome of the study is defined as compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result, or compensation in the form of an equity interest in the sponsor of the study, or in the form of compensation tied to sales of the product, such as royalty interest?)

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

F. EMERGENCY CONTACT INFORMATION AND PROCEDURES

1. In case of an emergency, the Investigator or Sub-Investigator can be reached at the following phone numbers.
- Office Number 386-366-6400
- Mandatory 24-Hour Number 386-366-6400
- Pager Number 386-214-9437
2. Should an emergency occur at your site, how close is the nearest hospital emergency room?
- 2 miles
3. ☒ No ☐ Yes Do you have privileges at the above-mentioned hospital?
- Please list other hospitals where you have privileges and the distance from your facility?
- Hospital Name _____ Distance _____
- Hospital Name _____ Distance _____
4. ☒ No ☐ Yes If you do not have privileges at a hospital, does a Sub-Investigator have privileges?
- Hospital Name _____ Distance _____
- If you or a Sub-Investigator do not have privileges, please attach an SOP for handling emergencies. Please see attached SOP regarding emergency procedures.***
5. What is the response time for a 911 call 3-5 minutes
6. Describe on-site emergency treatment equipment/personnel available for subjects. Please include a listing of the emergency medications on hand. (Use a separate sheet of paper, if necessary.)

EpiPen Auto-Injector (Epinephrine Hydrochloride) Single 0.3 mg dose [0.3 ml], Dey, Adrenalin Chloride Solution (1:1000) (of epinephrine), Monarch or nonproprietary, Aspirin 325 mg, Atropine Sulfate Injection, 1 mg (0.1mg/mL), Hospira or nonproprietary name, Naloxone Hydrochloride Injection, 0.4 mg/mL, Hospira, IMS or nonproprietary name, 2% Lidocaine Hydrochloride Injection, Hospira or nonproprietary name, Diphenhydramine Hydrochloride Capsules, 25 mg, Benedryl Allergy Kapseals or nonproprietary name, 50% Dextrose Injection, Abraxis or nonproprietary name,



Nitroglycerin, Sub Lingual Tablets, 0.4 mg or NitroQuickTM, Ethex or NitrostatTM, Pfizer or NitrotabTM, Able Albuterol Aerosol or Proventil HFA, Schering or Ventolin HFA, GlaxoSmithKline or nonproprietary name, Ammonia Inhalants, Silver Nitrate Applicators, Ativan (Lorazepam) Injection, 2mg/mL or same class (20mg/10mL vial)

(Diphenhydramine (or its equivalent), oxygen, IV Fluids, and epinephrine (or its equivalent) **MUST** be included at sites *where dosing with study drug is performed*.)

G. SUBJECT RECRUITMENT

1. How will subjects be recruited for this study?

☐ Existing Patients ☐ Referrals ☒ Other database
☒ Advertisements (i.e., newspaper, TV, radio, posters, internet, newsletters, brochures, flyers)

2. Will a screening script be utilized for this study?

☐ No ☒ Yes If yes, please submit the screening script for review.

All advertisements and recruitment materials must be reviewed and approved by the IRB prior to use.

PLEASE NOTE THAT THIS IRB DOES NOT APPROVE THE WORDS "FREE," "PAY," "PAID," OR "PAYMENT" IN ANY RECRUITMENT MATERIAL.

H. SUBJECT INFORMATION

1. Subjects for this study will be recruited from the following groups.

☐ Gender ☒ Male ☒ Female
☐ Ethnic Backgrounds ☒ Caucasian ☒ African-American ☒ Asian-American
☒ Native-American ☒ Hispanic ☒ Other as determined by subject
☐ Economic Status ☒ Upper Income ☒ Middle Income ☒ Lower Income

I. VULNERABLE POPULATIONS

1. Identify any vulnerable populations that are included in the study design, per the protocol:

☐ Children – include page number in protocol where identified _____
☐ Students (participating in research sponsored by the college/university they currently attend) – include page number in protocol where identified _____
☐ Economically disadvantaged – include page number in protocol where identified _____
☐ Educationally disadvantaged – include page number in protocol where identified _____
☐ Illiterate – include page number in protocol where identified _____
☐ Persons with limited capacity to consent – include page number in protocol where identified _____
☐ Terminally ill – include page number in protocol where identified _____
☐ Employees of the Principal Investigator/sponsor – include page number in protocol where identified _____
☒ None
☐ Other (describe) _____ include page number in protocol where identified _____

2. ☐ No ☐ Yes If any vulnerable populations are identified above, are the safeguards to protect these participants identified in the protocol? If yes, include page numbers where identified _____



If enrolling vulnerable populations into the study please describe in detail, on a separate page, the additional safeguards you will use to protect the rights and welfare of these subjects.

J. INFORMED CONSENT

1. Describe the Informed Consent process at this site by answering the following questions. Also, if you have an SOP, please attach. **Covance consent SOP is on file.**
 - a. Will the consent discussion with the potential subject take place in a private area at your site?
☐ No ☒ Yes If no, please attach a written explanation.
 - b. Identify all individuals at your site authorized to conduct the consent discussion with potential subjects.
☒ PI ☒ Sub I ☒ Research Coordinator ☒ Study Nurse ☒ Other trained staff _____
 - c. Identify the education on conducting a consent discussion that has been provided to the individuals identified above.
☒ In-house Education ☐ Role Play ☒ Education provided by a professional association
☒ Education provided by Sponsor/CRO ☒ Job Orientation ☒ Other _SOP training_
 - d. How long will the potential subject be allowed to review the Informed Consent document?
☒ As long as needed ☐ Overnight
☐ During the study visit ☐ Other _____
 - e. Will the PI or Sub-Investigator be available to answer subject questions during the consent process?
☐ No ☒ Yes If no, please attach a written explanation.
2. ☒ No ☐ Yes Do you anticipate enrolling any non-English speaking subjects?
If yes, what language? _____. Please note, the Informed Consent will need to be translated into this language.
3. ☐ No ☐ Yes Do you have someone who is fluent in the language of the non-English speaking subjects you plan to enroll? If no, how do you plan to provide Informed Consent to this person?

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

4. ☐ No ☒ Yes Will the subjects be compensated for their participation in this study?
If yes, please state specifically what the compensation will be. For example, what will the subject receive for each visit and the total amount they will receive if they complete the entire study. If necessary, attach a separate sheet of paper.

Please see attached draft ICF for compensation breakdown _____

5. With regard to the research-related injury section of the Informed Consent, is there an Investigator's Agreement or Contract with the Sponsor that outlines the provisions in place to pay for medical care should a subject become injured? ☐ No ☒ Yes If yes, please provide that verbiage for Board's review. If no, please ensure that verbiage provided in your Informed Consent is adequate. ***Please see consent SOP on file, and the language in the ICF is adequate and has been approved by the study sponsor.***

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

Please provide a description of the consent process including:

1. Who will be conducting the consent discussion? _screening staff_____
2. Who will provide consent or permission: ☒ subject ☐ LAR ☐ parent ☐ other: _____



3. What steps are taken to minimize the possibility of coercion or undue influence? please see consent SOP on file

4. Will there be any situations in which consent will be obtained from a Legally Authorized Representative (LAR) rather than the participant? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the participant to their participation in the procedures involved in this study.

If you are unsure of the answer to this question, it is recommended that you obtain legal advice.

5. If your site will be enrolling children, will there be any situations in which a legal guardian can provide permission for the child's participation? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the child to general medical care. *If you are unsure of the answer to this question, it is recommended that you obtain legal advice.*

In order to for the IRB to determine whether the regulatory criteria pertaining to the consent process are met, please check the following that apply for your site.

- ☒ The investigator will obtain the legally effective consent of the participant or the participant's legally authorized representative.
- ☒ The circumstances of the consent process provide the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate.
- ☒ The circumstances of the consent process minimize the possibility of coercion or undue influence.
- ☒ The individuals communicating information to the participant or the legally authorized representative during the consent process provide that information in language understandable to the participant or the representative.
- ☒ The information to be communicated to the participant or the representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative is made to waive or appear to waive any of the participant's legal rights.
- ☒ The information to be communicated to the participant or the legally authorized representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative releases or appears to release the investigator, the sponsor, MLIRB, or its agents from liability for negligence.
- ☒ The subject, or the subject's legally authorized representative, will sign and date the consent form and receive a signed and dated copy of the consent form to keep
- ☐ Will you be utilizing a short form consent document? ☒ No ☐ Yes If no, move onto section "K".
If yes, the following regulatory criteria must be met.

- ☐ The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative.
- ☐ A written summary embodies the basic and appropriate additional elements of disclosure.
- ☐ There will be a witness to the oral presentation.
- ☐ For participants who do not speak English, the witness will be conversant in both English and the language of the participant.
- ☐ The participant or the participant's legally authorized representative will sign the consent document.
- ☐ If the research is FDA-regulated, the participant or the participant's legally authorized representative will sign and date the consent document.
- ☐ The witness will sign both the short form and a copy of the summary.
- ☐ The person actually obtaining consent will sign a copy of the summary.
- ☐ A copy of the short form will be given to the participant or the participant's legally authorized representative.



☐ A copy of the summary will be given to the participant or the participant's legally authorized representative.

K. MONITORING PLAN

MLIRB requires adequate provisions for monitoring the data to ensure the safety and protection of study participants.

A. Identify your monitoring plan.

☐ Data and Safety Monitoring Board (DSMB)

☒ Is the plan detailed in the protocol? ☐ No ☒ Yes

If yes, include page number in protocol where identified. **Section 10.1**

If no, please provide this information as an attachment.

☐ Other (describe in detail)

☐ None (provide rationale)

L. MANAGEMENT OF INFORMATION

Describe the plan for management of information that is relevant to the protection of the participants, such as reporting of: (Use a separate sheet of paper, if necessary.)

1. Unanticipated problems involving risks to participants or others **Unanticipated problems will be reported to the IRB if the PI deems them reportable. Sites will be required to assess why the issue occurred and come up with a plan to ensure it does not happen again.**

2. Interim Results **Interim Results are not required for this study.**

3. Protocol Modifications **Protocol amendments and letters of administrative change will be submitted to the IRB for review and approval. Sites will be trained an applicable changes.**

M. BILLING INFORMATION

The party responsible for payment of MLIRB fees for this study at your site is

Site or Company name Covance CRU, Inc. Attention Heather Camilo

Address 1900 Mason Ave, Suite 140

Phone 386-366-6405 FAX 386-274-1258 Email heather.camilo@covance.com

N. SECURITY AND CONFIDENTIALITY

What precautions will be used to maintain the confidentiality and security of study records at your site? **(Please check all that apply.)**

☒ Paper-base records will be kept in a secure location and will be accessible only to personnel involved in this study.

☒ Computer-based files will be available only to personnel involved in this study through the use of access privileges and passwords.

☒ Prior to accessing any study-related information, site personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information.

☒ Whenever feasible, identifiers will be removed from study-related information.

☐ Other, please specify. _____

**U. PRIVACY**

Privacy refers to persons and people have an interest in controlling access to themselves, including the time they give the information, the place they given information, the nature of the information being given, and the nature of the research experience.

Please describe provisions to protect the privacy interests of study participants.

- ☐ No ☒ Yes Will the study participants be consented in a private area away from the public?
- ☐ No ☒ Yes Will study-related assessments be conducted in a private area?
- ☐ No ☒ Yes Will the private information collected be limited to what is required in the research study?
- ☐ No ☒ Yes Are there any additional provisions in place for protecting the privacy of the study participants?
- ☐ No ☐ Yes If "No" was answered to any of the above, please provide an explanation on a separate sheet of paper.

P. PRINCIPAL INVESTIGATOR STATEMENT AND SIGNATURE

As Principal Investigator, I agree

- that all of the information reported in this document is correct and I will not make any changes in the conduct of the research without prior approval from MLIRB;
- to abide by all of my responsibilities as outlined in the federal regulations and all applicable state and local laws;
- to report all changes in research activities and unanticipated problems involving risk to human subjects or others;
- to ensure that the privacy of study participants is protected;
- to ensure procedures are in place to maintain the confidentiality of the research data;
- to promptly report to MLIRB findings that could affect the safety of the study participants, influence the conduct of the study, or alter MLIRB approval to continue the study;
- to report safety information to MidLands which may help to provide additional protections for study participant's safety and well-being. Such reports include, but are not limited to, summaries from data safety monitoring groups (e.g., data monitoring committee, data and safety monitoring board, or data and safety monitoring committee; and
- to communicate to study participants any information that may directly affect participant safety, medical care, or willingness to continue participation.

I have read the MLIRB "Guidelines for Investigators" and agree to operate in compliance with MLIRB procedures set forth.

I understand that MLIRB, or one of its representatives, reserves the right to visit this study site at any time, with or without appropriate notice.


Principal Investigator Signature

27 JUN 2013
Date

H. Frank Farmer Jr.
Principal Investigator Printed Name



8417 Santa Fe, Suite 100, Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999
www.MLIRB.com

INVESTIGATOR REQUEST FOR APPROVAL/FACILITY DESCRIPTION

This form **must** be completed in its entirety and returned to the IRB before your study can be considered for review.
Failure to complete all items may result in delays in your approval.

Please complete a Supplemental Investigator Request for Approval/Facility Description form for **EACH additional site where subjects will be seen or as listed on Section 3 of the FDA Form 1572 for this study.** This form can be found on our website at www.MLIRB.com.

SPONSOR Philip Morris Products S.A. PROTOCOL NUMBER ZRHM-REXA-08-US
PRINCIPAL INVESTIGATOR NAME William Lewis, MD.

A. STUDY INFORMATION**TYPE OF STUDY**

1. ☐ No ☒ Yes Is this study regulated by the FDA? If not, please specify agency: _____
2. ☐ No ☒ Yes Is this a drug study? If no, go to Question No. 3
- ☒ No ☐ Yes Is this study being conducted under an IND?

What was the Date of the IND Submission?

*If yes, please provide one of the following

- ☐ Approval letter from the FDA indicating the IND number
- ☐ Letter from the Sponsor indicating the IND number
- ☐ Sponsor protocol indicating IND number
- ☐ Other (such as IND number indicated in correspondence from Sponsor)

If no, does the study meet the criteria identified in 21 CFR Part 312.2(b)?

- ☐ No ☒ Yes If no, the study must be conducted under an IND.

3. Is this a device study?

- ☒ No ☐ Yes If no, go to question 4.
- ☐ No ☐ Yes Is this study being conducted under an IDE?

If yes, please provide one of the following

- ☐ IDE Approval letter from the FDA
- ☐ Letter from the Sponsor indicating the IDE approval
- ☐ Copy of Humanitarian Device Exemption (HDE) approval letter from FDA

4. ☒ No ☐ Yes Is this study federally funded?

If yes, please provide the following information

- a. Are you the Grant holder? ☐ No ☐ Yes
- b. Agency(ies) receiving federal funds: _____
- c. Copy of the Grant
- d. The DHHS-approved sample Informed Consent document (if applicable)
- e. The DHHS-approved Protocol (if applicable)



5. Therapeutic Area

- ☐ Allergy/Asthma ☐ Cardiology ☐ CNS (Central Nervous System) ☐ Dermatology
☐ Immunology ☐ Inflammatory/Autoimmune ☐ Neurology ☐ Oncology
☒ Pulmonary ☐ Rheumatology ☐ N/A ☐ Other: _____

6. What is the indication of the study drug or device?

Smoking

7. Is this study? (Please check all the apply)

- ☒ Phase I - normal healthy subjects ☐ Phase I – patients ☐ Phase II
☐ Phase III ☐ Phase IIIb ☐ Phase IV ☐ Nutritional/Food Supplement
☐ Cosmetic ☐ Social Science ☐ Behavioral Science
☐ Other: _____

8. ☒ No ☐ Yes Is this the first time this drug will be given to humans?9. ☒ No ☐ Yes Is this study a medical device study? **If no, go to section B. SITE INFORMATION**

If yes, please provide the following information

- ☐ Statement of Investigator's commitment to the sponsor, per 21 CFR 812.43(a)(4)
☐ Report of prior investigations, if applicable
☐ Device information (for example, directions for use, user's manual, etc.), if applicable

Has the study been determined, by the Sponsor, to be ☒ Significant Risk ☐ Non-Significant Risk

☐ No ☒ Yes If Significant Risk, does the device meet the criteria in Title 21 CFR 812.3(m)?

If no, the device must be submitted as non-significant risk and you must provide a letter from the Sponsor indicating that the device is a non-significant risk and why it was determined to be so.

If yes, identify one of the following you are providing to the IRB

- ☐ Approval letter from the FDA indicating IDE number
☐ Letter from the Sponsor indicating the IDE number
☐ Sponsor protocol indicating IDE number
☐ Other (such as IDE number indicated in correspondence from Sponsor)

☐ No ☐ Yes Has the device been cleared/approved for marketing?

☐ No ☐ Yes If yes, is it being used in accordance with its cleared/approved labeling?

B. SITE INFORMATION

FACILITY NAME Covance Clinical Research Unit, Inc.

ADDRESS 1341 W. Mockingbird Lane Ste. 300E and 400E

CITY Dallas STATE TX ZIP CODE 75247

1. ☐ No ☒ Yes Is this the address where all correspondence should be sent?

If no, please list the address where the correspondence should be sent.



2. SETTING OF THE STUDY SITE

- ☐ Single Office Practice ☐ University Research Center ☒ Research Facility
☐ Multi-Office Practice ☐ Hospital ☐ Other _____

3. ☒ No ☐ Yes Has this protocol ever been submitted to another IRB for review?
If yes, please provide explanation on a separate sheet of paper.
4. ☒ No ☐ Yes Does a local IRB have jurisdiction over this site?
If yes, please attach a waiver form from the local IRB delegating responsibility to MLIRB.
The waiver form can be found on our website at www.midlandsirb.com.
5. ☐ No ☒ Yes Is there a specific person assigned to coordinate this study? If yes, please list the name
and title of this person and the telephone number where he/she can be reached.

Name Jasmine Ropers Title Project Manager Phone Number 608-310-8280

6. Estimate the number of personnel to be involved in conducting this study at your site(s), including the Principal Investigator and Sub-Investigators. 60
7. ☐ No ☒ Yes Is there a secure (locked) area for storage of the study drug?
If no, where do you store the drug? _____
8. ☒ No ☐ Yes Are there any community attitudes (religious, ethical, ethnic, or economic) that will affect
the conduct of research at this site? If yes, the attitudes are ☒ Positive ☐ Negative ☐ Neutral
If negative, please attach an explanation on a separate piece of paper.

C. PRINCIPAL INVESTIGATOR INFORMATION

1. ☐ No ☒ Yes Are you currently licensed to practice in the state where this study will be conducted?
State TX License No. F4212 Expiration 28Feb2014
2. ☐ No ☐ Yes Has your license to practice ever been suspended, revoked, or are there any restrictions on
your license? If so, please provide any documentation.
3. How long have you been conducting research? 6 years
4. What training have you had in the protection of human research subjects? (check all that apply)
- ☐ None ☒ Training by the Sponsor (i.e. Investigator meetings)
☐ OHRP Training Modules ☒ NIH Human Participant Protections Education
☒ Certified Investigator Training Initiative (CITI) ☐ DIA; Certified Clinical Investigator (CCI)
☐ ACRP; Certified Clinical Trial Investigator ☐ SoCRA; Clinical Research Professional (CRP)

Please provide a detailed description of the training that study personnel have received in Good Clinical Practice and Human Subject Protection. If you or your study staff have not had appropriate training, courses are provided at no cost to you on the MLIRB website under the "Training" link. The courses are through the Collaborative IRB

Training Initiative Program (CITI) in the Protection of Human Research Subjects. Login using MidLands as the institution.

5. In how many research studies are you currently listed as the Principal Investigator? Approximately 10
6. State the number of key staff who will assist in this research study
- | | |
|-----------|--|
| <u>2</u> | Sub-Investigators |
| <u>2</u> | Clinical Research Coordinators |
| <u>3</u> | Pharmacists |
| <u>48</u> | Other (e.g., laboratory specialists, regulatory specialists) |

Please provide a summary of the qualifications for the above-listed study staff. If necessary, attach a separate sheet



7. ☐ No ☒ Yes Have you or your site(s) been audited by the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP) in the past 5 years?
- If Yes, what were the date(s)? 28Feb2011, 11Apr2011
- If yes, was a Form FDA 483 or other list of observations issued? ☐ No ☒ Yes
- If yes, please provide a copy of the Form FDA 483 /list of observations and response letter. **Previously Provided to MLIRB**
8. ☒ No ☐ Yes Has the FDA ever issued a Warning Letter to you or your study site(s)?
9. ☒ No ☐ Yes Has FDA or OHRP ever terminated any study, or research, your site(s) has participated in, or sanctioned any Principal Investigator, Co-Investigator, or Sub-Investigator at your site?
10. ☒ No ☐ Yes Has any IRB ever withheld or withdrawn your approval as an Investigator?
11. ☒ No ☐ Yes Will a Sub-Investigator be performing study-related procedures that you are not qualified through expertise to perform? If yes, please provide copies of CV(s) and License(s).

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

MASSACHUSETTS INVESTIGATORS ONLY

1. Check here if you are registered with the Massachusetts Department of Public Health to dispense investigational drugs and attach a copy of your current registration.

Research License Number _____ Date of Expiration _____

2. Check here if you are not registered. Please contact the Massachusetts Department of Public Health at (617) 983-6712 for information on obtaining a registration.

Please note that an audit by MLIRB will be performed at your site in accordance with our affiliation agreement with the state of Massachusetts.

D. STATE LAWS

1. ☒ No ☐ Yes Are there any specific state or local regulations/laws governing research in your state? For example, California requires the "California Experimental Bill of Rights." (If you are unsure, please contact your local or state government.)

If yes, please describe _____

2. What is the age of consent in your state for treatment or procedures involved in this research study? 18

3. ☒ No ☐ Yes Does your state or local laws require additional information beyond those required by FDA/OHRP to be in the informed consent (to be legally effective)?

If yes, please explain. Attach additional paperwork, if necessary. _____

E. FINANCIAL DISCLOSURE

During the past year, has any Investigator or Investigators spouse, domestic partner or children, or any person involved in this research study:

1. ☒ No ☐ Yes Been an officer, director, or employee of the sponsor of this research study?
2. ☒ No ☐ Yes Held a significant equity interest in the sponsor of this research study? A significant equity interest would mean any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds \$5,000 aggregated by immediate family member during the time the clinical investigator is carrying out the study and for 1 year following completion of the study. Has any arrangement been made where the value of the ownership interests will be affected by the outcome of the research or exceeds 5% interest in any one single entity when aggregated for the immediate family?
3. ☒ No ☐ Yes Had any propriety interest in the research product for this research study a proprietary interest in the product is defined as property or other financial interest including, but not limited to, a patent, trademark, copyright, or licensing agreement?



4. ☒ No ☐ Yes Received, or made any arrangement to receive, any significant payments of other sorts from the sponsor of this research study to support activities of the investigator that have a monetary value of more than \$5,000 aggregated by immediate family member exclusive of the costs of conducting the research study, such as retainers for ongoing consultation or honoraria, during the course of the study?
5. ☒ No ☐ Yes Agreed to, or plan to, accept recruitment bonuses for enrolling subjects into this research study?
6. ☒ No ☐ Yes Entered into any financial arrangement for this research study whereby the value of compensation paid could affect the outcome of this study (compensation affected by the outcome of the study is defined as compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result, or compensation in the form of an equity interest in the sponsor of the study, or in the form of compensation tied to sales of the product, such as royalty interest?)

If you answered yes to any of the above, you must provide an explanation and any pertinent documentation.

F. EMERGENCY CONTACT INFORMATION AND PROCEDURES

1. In case of an emergency, the Investigator or Sub-Investigator can be reached at the following phone numbers.
- Office Number 214-647-9300
- Mandatory 24-Hour Number 972-955-5373
- Pager Number _____
2. Should an emergency occur at your site, how close is the nearest hospital emergency room?
- 2 miles
3. ☒ No ☐ Yes Do you have privileges at the above-mentioned hospital?
- Please list other hospitals where you have privileges and the distance from your facility?
- Hospital Name _____ Distance _____
- Hospital Name _____ Distance _____
4. ☒ No ☐ Yes If you do not have privileges at a hospital, does a Sub-Investigator have privileges?
- Hospital Name _____ Distance _____
- If you or a Sub-Investigator do not have privileges, please attach an SOP for handling emergencies.*
5. What is the response time for a 911 call under 5 minutes (average 4:16)
6. Describe on-site emergency treatment equipment/personnel available for subjects. Please include a listing of the emergency medications on hand. (Use a separate sheet of paper, if necessary.)
- ACLS Certified personnel, AED, EpiPen Auto Injector (Adult) Single 0.3mg dose (0.3ml), Epinephrine 1:1000 (1mg/ml), Aspirin 325mg tablets, Atropine Sulfate INJ 1mg (0.1mg/ml), Naloxone HCl INJ 0.4mg/ml, Lidocaine HCl INJ 2%, Diphenhydramine HCL 25mg capsules, Diphenhydramine HCL INJ 50mg/ml vial, Dextrose INJ 50%, Nitroglycerine Sub Lingual Tablets 0.4mg tablets, Albuterol Aerosol (albuterol sulfate) 200 metered inhalations, Ammonia Inhalants, Silver Nitrate Applicators, Diazepam INJ 5mg/ml, Epinephrine INJ, 1:10,000 1mg (0.1mg/ml), EpiPen Jr. Auto Injector, Single 0.15mg dose (0.15ml), Glucagon INJ 1mg/unit, SoluMedrol INJ 125mg/2ml, oxygen
- (Diphenhydramine (or its equivalent), oxygen, IV Fluids, and epinephrine (or its equivalent) **MUST** be included at sites *where dosing with study drug is performed*.)

G. SUBJECT RECRUITMENT

1. How will subjects be recruited for this study?

☒ Existing Patients ☐ Referrals ☐ Other _____



X Advertisements (i.e., newspaper, TV, radio, posters, internet, newsletters, brochures, flyers)

2. Will a screening script be utilized for this study?

☐ No ☒ Yes If yes, please submit the screening script for review.

All advertisements and recruitment materials must be reviewed and approved by the IRB prior to use.

PLEASE NOTE THAT THIS IRB DOES NOT APPROVE THE WORDS "FREE," "PAY," "PAID," OR "PAYMENT" IN ANY RECRUITMENT MATERIAL.

H. SUBJECT INFORMATION

1. Subjects for this study will be recruited from the following groups.

- X Gender ☐ Male ☐ Female
- X Ethnic Backgrounds ☐ Caucasian ☐ African-American ☐ Asian-American
- ☐ Native-American ☐ Hispanic ☐ Other _____
- ☐ Economic Status ☐ Upper Income ☐ Middle Income ☐ Lower Income

I. VULNERABLE POPULATIONS

1. Identify any vulnerable populations that are included in the study design, per the protocol:

- ☐ Children – include page number in protocol where identified _____
- ☐ Students (participating in research sponsored by the college/university they currently attend) – include page number in protocol where identified _____
- ☐ Economically disadvantaged – include page number in protocol where identified _____
- ☐ Educationally disadvantaged – include page number in protocol where identified _____
- ☐ Illiterate – include page number in protocol where identified _____
- ☐ Persons with limited capacity to consent – include page number in protocol where identified _____
- ☐ Terminally ill – include page number in protocol where identified _____
- ☐ Employees of the Principal Investigator/sponsor – include page number in protocol where identified _____
- X None
- ☐ Other (describe) _____ include page number in protocol where identified _____

2. ☐ No ☐ Yes If any vulnerable populations are identified above, are the safeguards to protect these participants identified in the protocol? If yes, include page numbers where identified _____

If enrolling vulnerable populations into the study please describe in detail, on a separate page, the additional safeguards you will use to protect the rights and welfare of these subjects.

J. INFORMED CONSENT

1. Describe the Informed Consent process at this site by answering the following questions. Also, if you have an SOP, please attach.

- a. Will the consent discussion with the potential subject take place in a private area at your site?
- ☐ No ☒ Yes If no, please attach a written explanation.
- b. Identify all individuals at your site authorized to conduct the consent discussion with potential subjects.
- X PI X Sub I X Research Coordinator X Study Nurse X Other Screening Coordinator
- c. Identify the education on conducting a consent discussion that has been provided to the individuals identified above.



- ☒ In-house Education ☐ Role Play ☐ Education provided by a professional association
☐ Education provided by Sponsor/CRO ☐ Job Orientation ☒ Other ICF Training

d. How long will the potential subject be allowed to review the Informed Consent document?

- ☒ As long as needed ☐ Overnight
☐ During the study visit ☐ Other _____

e. Will the PI or Sub-Investigator be available to answer subject questions during the consent process?

- ☐ No ☒ Yes If no, please attach a written explanation.

2. ☐ No ☒ Yes Do you anticipate enrolling any non-English speaking subjects?

If yes, what language? Spanish Please note, the Informed Consent will need to be translated into this language.

3. ☐ No ☒ Yes Do you have someone who is fluent in the language of the non-English speaking subjects you plan to enroll? If no, how do you plan to provide Informed Consent to this person?

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

4. ☐ No ☒ Yes Will the subjects be compensated for their participation in this study?

If yes, please state specifically what the compensation will be. For example, what will the subject receive for each visit and the total amount they will receive if they complete the entire study. If necessary, attach a separate sheet of paper. **Please see attached ICF for compensation breakdown**

5. With regard to the research-related injury section of the Informed Consent, is there an Investigator's Agreement or Contract with the Sponsor that outlines the provisions in place to pay for medical care should a subject become injured? ☐ No ☒ Yes If yes, please provide that verbiage for Board's review. If no, please ensure that verbiage provided in your Informed Consent is adequate.

A certified, translated Informed Consent must be approved by the IRB prior to use. A Certificate of Translation MUST accompany the Informed Consent.

Please provide a description of the consent process including:

1. Who will be conducting the consent discussion? Screening Coordinator, Clinical Research Coordinator, or assigned trained staff

2. Who will provide consent or permission: ☒ subject ☐ LAR ☐ parent ☐ other: _____

3. What steps are taken to minimize the possibility of coercion or undue influence? Appropriate staff training

4. Will there be any situations in which consent will be obtained from a Legally Authorized Representative (LAR) rather than the participant? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the participant to their participation in the procedures involved in this study.

If you are unsure of the answer to this question, it is recommended that you obtain legal advice.

5. If your site will be enrolling children, will there be any situations in which a legal guardian can provide permission for the child's participation? ☒ No ☐ Yes

If yes, describe the individuals that are authorized under state or other law to consent on behalf of the child to general medical care. *If you are unsure of the answer to this question, it is recommended that you obtain legal advice.*



In order for the IRB to determine whether the regulatory criteria pertaining to the consent process are met, please check the following that apply for your site.

- ☒ The investigator will obtain the legally effective consent of the participant or the participant's legally authorized representative.
- ☒ The circumstances of the consent process provide the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate.
- ☒ The circumstances of the consent process minimize the possibility of coercion or undue influence.
- ☒ The individuals communicating information to the participant or the legally authorized representative during the consent process provide that information in language understandable to the participant or the representative.
- ☒ The information to be communicated to the participant or the representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative is made to waive or appear to waive any of the participant's legal rights.
- ☒ The information to be communicated to the participant or the legally authorized representative during the consent process does not include exculpatory language through which the participant or the legally authorized representative releases or appears to release the investigator, the sponsor, MLIRB, or its agents from liability for negligence.
- ☒ The subject, or the subject's legally authorized representative, will sign and date the consent form and receive a signed and dated copy of the consent form to keep.
- ☐ Will you be utilizing a short form consent document? ☒ No ☐ Yes If no, move onto section "K".
If yes, the following regulatory criteria must be met.

- ☐ The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative.
- ☐ A written summary embodies the basic and appropriate additional elements of disclosure.
- ☐ There will be a witness to the oral presentation.
- ☐ For participants who do not speak English, the witness will be conversant in both English and the language of the participant.
- ☐ The participant or the participant's legally authorized representative will sign the consent document.
- ☐ If the research is FDA-regulated, the participant or the participant's legally authorized representative will sign and date the consent document.
- ☐ The witness will sign both the short form and a copy of the summary.
- ☐ The person actually obtaining consent will sign a copy of the summary.
- ☐ A copy of the short form will be given to the participant or the participant's legally authorized representative.
- ☐ A copy of the summary will be given to the participant or the participant's legally authorized representative.

K. MONITORING PLAN

MLIRB requires adequate provisions for monitoring the data to ensure the safety and protection of study participants.

A. Identify your monitoring plan.

- ☐ Data and Safety Monitoring Board (DSMB)

☒ Is the plan detailed in the protocol? ☐ No ☒ Yes

If yes, include page number in protocol where identified. Section 10.1

If no, please provide this information as an attachment.

- ☐ Other (describe in detail)
- ☐ None (provide rationale)

L. MANAGEMENT OF INFORMATION

Describe the plan for management of information that is relevant to the protection of the participants, such as reporting of: (Use a separate sheet of paper, if necessary.)



1. Unanticipated problems involving risks to participants or others Will follow MidLands IRB requirements
2. Interim Results Will follow MidLands IRB requirements
3. Protocol Modifications Will follow MidLands IRB requirements

M. BILLING INFORMATION

The party responsible for payment of MLIRB fees for this study at your site is

Site or Company name Covance Clinical Research Unit, Inc. Attention Shannon Perez

Address 1341 W. Mockingbird Lane, Ste. 400E, Dallas, TX 75247

Phone 214-647-3949 FAX 214-920-9057 Email shannon.perez@covance.com

N. SECURITY AND CONFIDENTIALITY

What precautions will be used to maintain the confidentiality and security of study records at your site? **(Please check all that apply.)**

- ☒ Paper-base records will be kept in a secure location and will be accessible only to personnel involved in this study.
- ☒ Computer-based files will be available only to personnel involved in this study through the use of access privileges and passwords.
- ☒ Prior to accessing any study-related information, site personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information.
- ☒ Whenever feasible, identifiers will be removed from study-related information.
- ☐ Other, please specify. _____

O. PRIVACY

Privacy refers to persons and people have an interest in controlling access to themselves, including the time they give the information, the place they given information, the nature of the information being given, and the nature of the research experience.

Please describe provisions to protect the privacy interests of study participants.

- ☐ No ☒ Yes Will the study participants be consented in a private area away from the public?
- ☐ No ☒ Yes Will study-related assessments be conducted in a private area?
- ☐ No ☒ Yes Will the private information collected be limited to what is required in the research study?
- ☐ No ☒ Yes Are there any additional provisions in place for protecting the privacy of the study participants?
- ☐ No ☐ Yes If "No" was answered to any of the above, please provide an explanation on a separate sheet of paper.

P. PRINCIPAL INVESTIGATOR STATEMENT AND SIGNATURE

As Principal Investigator, I agree



- that all of the information reported in this document is correct and I will not make any changes in the conduct of the research without prior approval from MLIRB;
- to abide by all of my responsibilities as outlined in the federal regulations and all applicable state and local laws;
- to report all changes in research activities and unanticipated problems involving risk to human subjects or others;
- to ensure that the privacy of study participants is protected;
- to ensure procedures are in place to maintain the confidentiality of the research data;
- to promptly report to MLIRB findings that could affect the safety of the study participants, influence the conduct of the study, or alter MLIRB approval to continue the study;
- to report safety information to MidLands which may help to provide additional protections for study participant's safety and well-being. Such reports include, but are not limited to, summaries from data safety monitoring groups (e.g., data monitoring committee, data and safety monitoring board, or data and safety monitoring committee; and
- to communicate to study participants any information that may directly affect participant safety, medical care, or willingness to continue participation.

I have read the MLIRB "Guidelines for Investigators" and agree to operate in compliance with MLIRB procedures set forth.

I understand that MLIRB, or one of its representatives, reserves the right to visit this study site at any time, with or without appropriate notice.

①

Principal Investigator Signature

02 Jun 2013

Date

William Lewis, MD

Principal Investigator Printed Name

① Duplicate signature. Please Refer to page 10 of 10 dated 28 JUN 2013.
HE11amay2016



- that all of the information reported in this document is correct and I will not make any changes in the conduct of the research without prior approval from MLIRB;
- to abide by all of my responsibilities as outlined in the federal regulations and all applicable state and local laws;
- to report all changes in research activities and unanticipated problems involving risk to human subjects or others;
- to ensure that the privacy of study participants is protected;
- to ensure procedures are in place to maintain the confidentiality of the research data;
- to promptly report to MLIRB findings that could affect the safety of the study participants, influence the conduct of the study, or after MLIRB approval to continue the study;
- to report safety information to Midlands which may help to provide additional protections for study participant's safety and well-being. Such reports include, but are not limited to, summaries from data safety monitoring groups (e.g., data monitoring committee, data and safety monitoring board, or data and safety monitoring committee; and
- to communicate to study participants any information that may directly affect participant safety, medical care, or willingness to continue participation.

I have read the MLIRB "Guidelines for Investigators" and agree to operate in compliance with MLIRB procedures set forth.

I understand that MLIRB, or one of its representatives, reserves the right to visit this study site at any time, with or without appropriate notice.

William Lewis
Principal Investigator Signature

28 Jan 2013
Date

William Lewis, MD
Principal Investigator Printed Name



16.1.3.11 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 001 SUBMISSION LETTER (LOCAL LANGUAGE)

Not applicable.



16.1.3.12 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 001 APPROVAL (ENGLISH)



July 2, 2013

William Lewis, M.D.
Covance Clinical Research Unit, Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Dear Dr. Lewis:

The MidLands Independent Review Board (MLIRB) met on this date and reviewed the Clinical Study Protocol ZRHM-REXA-08-US, Version number: Final 1.0, Revision date: 26 June 2013, entitled "A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting." A quorum was present. A copy of the IRB membership list is enclosed.

The IRB approved the Clinical Study Protocol without modification.

The IRB reviewed the THS 2.2 Menthol Investigator's Brochure, Version number: Version 1.0, Edition number: Edition 1, Release date: 11 April 2013, as well as the User Manual for Tobacco Heating Device (Model 2.2) ©2013.

The IRB reviewed your credentials and site(s) information and approved you to conduct the study as Principal Investigator at the site(s) indicated below:

Covance Clinical Research Unit, Inc.
1341 W. Mockingbird Lane, Suite 400E & 300E
Dallas, TX 75247

The IRB reviewed and approved the "Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with modifications and determined that the Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent guidelines (21 CFR Part 50) and ICH Guidelines. Copies of the "Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with revisions shown are enclosed.

Copies of the revised approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1, dated 07/02/13), "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1, dated 07/02/13) and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1, dated 07/02/13) stamped by the MLIRB are also enclosed.



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 2

The Board reviewed and approved the following documents without modification:

- "Product Use Questionnaire"
- "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011)
- "Cough Assessment" with Translation Certifications (English into United States Spanish) as well as (English in to United States English)
- "Fagerstrom Test for Nicotine Dependence" with Translation Certifications (English into United States Spanish) as well as (English in to United States English)
- "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" (English)
- "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" with Translation Certifications (English into United States Spanish)
- "Prochaska 'Stage of Change' Questionnaire"
- "Modifier Cigarette Evaluation Questionnaire (mCEQ)" (English)
- "Modifier Cigarette Evaluation Questionnaire (mCEQ)" with Translation Certifications (English into United States Spanish)
- HST Questionnaire" (Version 2.0 18/APR/2013)

Copies of the above approved documents stamped by MLIRB are enclosed.

The IRB must review and approve the produced video/audio prior to broadcast. Please submit to the IRB as soon as possible.

Continuing review of this clinical trial must take place at intervals appropriate to the degree of risk. The IRB has determined that you must submit a report on the progress of this study annually from your approval date. Continuing approval of the clinical trial is contingent upon receipt of the report by this IRB.

This study is approved and you may commence (start) the research.

APPROVAL DATE: JULY 2, 2013

EXPIRATION DATE: JULY 1, 2014

In addition to submitting an annual report, your responsibilities as Principal Investigator are indicated in the attached MLIRB "Guidelines for Investigator." Please read this document. These guideline can also be found on our website at www.mlirb.com.

The aforementioned approvals are conditional upon the completion of any pre-investigational requirements by the U.S. Food and Drug Administration.

MLIRB operates in compliance with federal regulations governing Independent Review Boards set forth in 21 CFR Part 56 and regulations governing Informed Consent set forth in 21 CFR Part 50, and the Department of Health and Human Services 45 CFR Part 46. MLIRB is also in compliance with ICH Guidelines for Good Clinical Practice.



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 3

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1) stamped by MLIRB
"Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1) stamped by MLIRB
Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1) stamped by MLIRB
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Approved HST Questionnaire" (Version 2.0 18/APR/2013) stamped by MLIRB
User Manual for Tobacco Heating Device (Model 2.2) ©2013 stamped by MLIRB
MLIRB Membership List
MLIRB "Guidelines for Investigators"

cc: Celisa Tolan, Covance Clinical Research Unit, w/enclosures



July 2, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Dear Dr. Farmer:

The MidLands Independent Review Board (MLIRB) met on this date and reviewed the Clinical Study Protocol ZRHM-REXA-08-US, Version number: Final 1.0, Revision date: 26 June 2013, entitled "A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting." A quorum was present. A copy of the IRB membership list is enclosed.

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1900 Mason Ave., Ste 140
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H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 2

The Board reviewed and approved the following documents without modification:

- "CoRA Script" (V3)
- "Subject Calendar Cohort 1" (Version 1, 26Jun2013)
- Advertisements (Print ad, :30 Radio ad, Abbreviated online ad, Online ad, and Abbreviated Ads – Outdoor)
- "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)"
- "Prochaska 'Stage of Change' Questionnaire"
- "Product Use Questionnaire"
- "SES Questionnaire"
- "Questionnaire on smoking urges (QSU)"
- "Meta-questionnaire"
- "Smoking Questionnaire"
- "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011)
- "Modifier Cigarette Evaluation Questionnaire (mCEQ)"
- HST Questionnaire" (Version 2.0 18/APR/2013)
- "Cough Assessment" with Translation Certification (English into United States English)
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This study is approved and you may commence (start) the research.

APPROVAL DATE: JULY 2, 2013

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In addition to submitting an annual report, your responsibilities as Principal Investigator are indicated in the attached MLIRB "Guidelines for Investigator." Please read this document. These guideline can also be found on our website at www.mlirb.com.

The aforementioned approvals are conditional upon the completion of any pre-investigational requirements by the U.S. Food and Drug Administration.

MLIRB operates in compliance with federal regulations governing Independent Review Boards set forth in 21 CFR Part 56 and regulations governing Informed Consent set forth in 21 CFR Part 50, and the Department of Health and Human Services 45 CFR Part 46. MLIRB is also in compliance with ICH Guidelines for Good Clinical Practice.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No. ZRHM-REXA-08-US
July 2, 2013
Page 3

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 1) stamped by MLIRB
"Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 1) stamped by MLIRB
Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 1) stamped by MLIRB
"Informed Consent Authorization to Participate in a Clinical Investigation," "Informed Consent Document for Genetic and Pharmacogenomic Analysis," and "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" with revisions shown
Approved "CoRA Script" (V3) stamped by MLIRB
Approved "Subject Calendar Cohort 1" (Version 1, 26Jun2013) stamped by MLIRB
Approved Advertisements (Print ad, :30 Radio ad, Abbreviated online ad, Online ad, and Abbreviated Ads – Outdoor) stamped by MLIRB
Approved "Minnesota Nicotine Dependence/Withdrawal Scale (MNWS)" stamped by MLIRB
Approved "Prochaska 'Stage of Change' Questionnaire" stamped by MLIRB
Approved "Product Use Questionnaire" stamped by MLIRB
Approved "SES Questionnaire" stamped by MLIRB
Approved "Questionnaire on smoking urges (QSU)" stamped by MLIRB
Approved "Meta-questionnaire" stamped by MLIRB
Approved "Smoking Questionnaire" stamped by MLIRB
Approved "Behavioral Risk Factor Surveillance System Questionnaire 2011" (2011 BRFSS/Final/January 27, 2011) stamped by MLIRB
Approved "Modifier Cigarette Evaluation Questionnaire (mCEQ)" stamped by MLIRB
Approved HST Questionnaire" (Version 2.0 18/APR/2013) stamped by MLIRB
Approved "Cough Assessment" stamped by MLIRB
Approved "Fagerstrom Test for Nicotine Dependence" stamped by MLIRB
User Manual for Tobacco Heating Device (Model 2.2) ©2013 stamped by MLIRB
MLIRB Membership List
MLIRB "Guidelines for Investigators"

cc: Heather Camilo, Covance CRU Inc., w/enclosures



**16.1.3.13 IRB SUBJECT INFORMATION AND INFORMED CONSENT
FORM VERSION 001 APPROVAL LETTER (LOCAL
LANGUAGE)**

Not applicable.



16.1.3.14 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM SUBMISSION LETTERS (ENGLISH)



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	20 Nov 2013
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI		
Fax	386-274-1258	Email	Heather.camilo@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	PMI		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	2013 to 2014
Primary contact person	Daytona Beach- Heather Camilo, Dallas- Celisa Tolan		

Change(s)

Brief description of changes being made	Protocol amendment, revised IB, revised ICF, questionnaires
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input checked="" type="checkbox"/> Investigator's Brochure <input checked="" type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input checked="" type="checkbox"/> Other (specify): questionnaires, draft revised ICF
Check all that apply	<input type="checkbox"/> This change does not increase risks to participants enrolled in the study <input checked="" type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain</i>



why the change is necessary (for example, the change is proposed by the sponsor):
All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	13 Dec 2013
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI		
Fax	386-274-1258	Email	Heather.camilo@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	PMI		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	2013 to 2014
Primary contact person	Daytona Beach- Heather Camilo, Dallas- Celisa Tolan		

Change(s)

Brief description of changes being made	Protocol amendment, revised ICF, protocol signature pages
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input type="checkbox"/> This change does not increase risks to participants enrolled in the study <input checked="" type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain</i>



why the change is necessary (for example, the change is proposed by the sponsor):
All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview	
Protocol #	ZHRM-REXA-08-US
Date of this request	14 Jan 2014
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI
Fax	386-274-1258
Email	Heather.camilo@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting
Sponsor	PMI
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial
Proposed study period	to
Current IRB approval period	2013 to 2014
Primary contact person	Daytona Beach- Heather Camilo
Change(s)	
Brief description of changes being made	Protocol amendment, revised ICF, revised ads, revised scripts
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input checked="" type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>



All revisions and additions are being submitted.

Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	14 Jan 2014
Principal Investigator Name and Site Address	William Lewis, MD		
Fax	214-920-9057	Email	celisa.tolan@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	Phillip Morris		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	02Jul2013 to 01Jul2014
Primary contact person	Celisa Tolan – Regulatory Specialist		

Change(s)

Brief description of changes being made	Protocol amendment, revised ICF, revised ads, revised scripts
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input checked="" type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>



All revisions and additions are being submitted.

Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview			
Protocol #	ZHRM-REXA-08-US	Date of this request	14April2014
Principal Investigator Name and Site Address	H. Frank Farmer, Jr, MD, PhD, FACP, CPI		
Fax	386-274-1258	Email	Regina.oegerle@Covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	Phillip Morris		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	17Dec2013 to 12June2014	Current IRB approval period	02-July-2013 to 01-July-2014
Primary contact person	Regina Oegerle		
Change(s)			
Brief description of changes being made	Revised Main ICF, Biobanking ICF, PGx ICF, Protocol Amendment, Protocol Amendment Signature Page		
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form(Main, PGx and Biobanking ICF) <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): _____ <input type="checkbox"/> Other (specify): _____		
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input type="checkbox"/> This change does not necessitate revision of the consent form document <input checked="" type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>		



Attach the sponsor's formal notice of a change or revised protocol, if applicable.



8417 Santa Fe, Suite 100; Overland Park, Kansas 66212
Telephone (913) 385-1414 FAX (913) 385-9999

APPLICATION FOR AMENDMENT

A study must be carried out in accordance with the protocol approved by the MLIRB. Any changes in the study, including "for example" changes in the subject population, recruitment plans, advertising materials, research procedures, sites or research personnel who are instrumental to the execution of the study, must be approved by the IRB prior to the change taking place.

When submitting a Request for Amendment, you need to submit for review only those documents that have been revised.

Study Overview

Protocol #	ZHRM-REXA-08-US	Date of this request	14Apr2014
Principal Investigator Name and Site Address	William Lewis, MD		
Fax	214-920-9057	Email	celisa.tolan@covance.com
Study Title	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting		
Sponsor	Phillip Morris		
Trial Type	<input type="checkbox"/> Single Center Trial <input checked="" type="checkbox"/> Multi-Center Trial		
Proposed study period	to	Current IRB approval period	02Jul2013 to 01Jul2014
Primary contact person	Celisa Tolan – Regulatory Specialist		

Change(s)

Brief description of changes being made	Protocol amendment V5, revised Main ICF, Biobanking ICF and PGx ICF
Indicate all changes you are proposing to make	<input checked="" type="checkbox"/> Change in currently approved protocol <input checked="" type="checkbox"/> Change in currently approved consent form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Form FDA 1572 <input type="checkbox"/> Recruitment Forms/Advertisements <input type="checkbox"/> Addition/Deletion of a Site <input type="checkbox"/> Additional Information (specify): <input type="checkbox"/> Other (specify):
Check all that apply	<input checked="" type="checkbox"/> This change does not increase risks to participants enrolled in the study <input type="checkbox"/> This change may increase risks to participants enrolled in the study <input checked="" type="checkbox"/> This change does not necessitate revision of the consent form document <input type="checkbox"/> Subjects already enrolled will be re-consented <i>If the change may increase risks to participants enrolled in the study, please explain why the change is necessary (for example, the change is proposed by the sponsor):</i>



All revisions and additions are being submitted.
Attach the sponsor's formal notice of a change or revised protocol, if applicable.



16.1.3.15 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM SUBMISSION LETTERS (LOCAL LANGUAGE)

Not applicable.



16.1.3.16 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM APPROVAL LETTERS (ENGLISH)



November 26, 2013

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis:

The MidLands Independent Review Board (MLIRB) met on this date to review the revised THS.2.2 Menthol Investigator's Brochure, Version number: Final 1.0, Edition number: Edition 2, Release date: 14 November 2013, the revised Clinical Study Protocol, Version number: Final 2.0, Revision date: 19 November 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ), Smoking questionnaire (SQ)) for the above-referenced study.

The IRB approved revised Clinical Study Protocol, Version number: Final 2.0, Revision date: 19 November 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation" as well as the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ), and "Smoking questionnaire (SQ))" without modification and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 2, dated 11/26/13) as well the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ), and "Smoking questionnaire (SQ))" stamped by the MLIRB are enclosed.



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
November 26, 2013
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Kathy Chase'.

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation"
(Version 2) stamped by MLIRB
Approved revised "Behavioral Risk Factor Surveillance System Questionnaire 2011" stamped
by MLIRB
Approved revised "Human Smoking Topography Questionnaire" stamped by MLIRB
Approved revised "Prochaska 'Stage of Change' Questionnaire" stamped by MLIRB
Approved revised "SES Questionnaire" stamped by MLIRB
Approved revised "Meta-questionnaire (to be answered after SQ)" stamped by MLIRB
Approved revised "Smoking questionnaire (SQ)" stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures



November 26, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

The MidLands Independent Review Board (MLIRB) met on this date to review the revised THS.2.2 Menthol Investigator's Brochure, Version number: Final 1.0, Edition number: Edition 2, Release date: 14 November 2013, the revised Clinical Study Protocol, Version number: Final 2.0, Revision date: 19 November 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ), Smoking questionnaire (SQ)) for the above-referenced study.

The IRB approved revised Clinical Study Protocol, Version number: Final 2.0, Revision date: 19 November 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation" as well as the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ), and "Smoking questionnaire (SQ)) without modification and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 2, dated 11/26/13) as well the revised questionnaires ("Behavioral Risk Factor Surveillance System Questionnaire 2011," "Human Smoking Topography Questionnaire," "Prochaska 'Stage of Change' Questionnaire," "SES Questionnaire," "Meta-questionnaire (to be answered after SQ), and "Smoking questionnaire (SQ))" stamped by the MLIRB are enclosed.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No. ZRHM-REXA-08-US
November 26, 2013
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in cursive script that reads 'Kathy Chase'.

Kathy Chase, Pharm. D.
Chairperson

KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation"
(Version 2) stamped by MLIRB
Approved revised "Behavioral Risk Factor Surveillance System Questionnaire 2011" stamped
by MLIRB
Approved revised "Human Smoking Topography Questionnaire" stamped by MLIRB
Approved revised "Prochaska 'Stage of Change' Questionnaire" stamped by MLIRB
Approved revised "SES Questionnaire" stamped by MLIRB
Approved revised "Meta-questionnaire (to be answered after SQ)" stamped by MLIRB
Approved revised "Smoking questionnaire (SQ)" stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures



December 13, 2013

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, as well as the revised "Informed Consent Authorization to Participate in a Clinical Investigation" for the above-referenced study.

I approved revised Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, without modification and the revised "Informed Consent Authorization to Participate in a Clinical Investigation" with modifications and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines. A copy of the "Informed Consent Authorization to Participate in a Clinical Investigation" with revision shown is enclosed.

A copy of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 3, dated 12/13/13) stamped by the MLIRB is also enclosed.

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 3)
stamped by MLIRB
"Informed Consent Authorization to Participate in a Clinical Investigation" with revisions shown

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosures



December 13, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well as the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" for the above-referenced study.

I approved revised Clinical Study Protocol Amendment N°1, Version: Final Version 3.0, Date: 11 December 2013, the revised Clinical Study Protocol, Version number: Final 3.0, Revision date: 11 December 2013, as well as the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" without modification and the revised "Informed Consent Authorization to Participate in a Clinical Investigation" with modifications and determined that the revised Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines. A copy of the "Informed Consent Authorization to Participate in a Clinical Investigation" with revisions shown is enclosed.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 3, dated 12/13/13) as well as the "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 2, dated 12/13/13) stamped by the MLIRB are also enclosed.

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 3) stamped by MLIRB
"Informed Consent Authorization to Participate in a Clinical Investigation" with revisions shown
Approved revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Version 2) stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures

8417 Santa Fe Drive Suite 100 Overland Park, KS 66212

Toll free: 800 636 4445 Phone: 913 385 1414 Fax: 913 385 9999 www.MLIRB.com



December 26, 2013

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

On this day, an administrative change was made to the "Informed Consent Authorization to Participate in a Clinical Investigation" document. It was noted the address incorrectly read as "13900 Mason Avenue" and should have read "1900 Mason Avenue." MLIRB has made this revision to the Informed Consent.

A copy of the approved revised "Informed Consent Authorization to Participate in a clinical Investigation" (Version 4, dated 12/26/13) stamped by MLIRB is enclosed.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Toni Gerrity, CIM, CIP
Manager of Operations

/tg

enclosure: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation"
(Version 4) stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosure



January 14, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the revised Clinical Study Protocol, Version number: Final 4.0, Revision date: 14 January 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) for the above-referenced study.

I approved revised Clinical Study Protocol, Version number: Final 4.0, Revision date: 14 January 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) without modification and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 4, dated 1/14/14) as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) stamped by the MLIRB are enclosed.



William Lewis, M.D.
Protocol No.: ZRHM-REXA-08-US
January 14, 2014
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in blue ink that reads 'Lynsey Hartman'.

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 4) stamped by MLIRB
Approved revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) stamped by MLIRB

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosures



January 14, 2014

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the revised Clinical Study Protocol, Version number: Final 4.0, Revision date: 14 January 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) for the above-referenced study.

I approved revised Clinical Study Protocol, Version number: Final 4.0, Revision date: 14 January 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) without modification and determined that the revised Informed Consent is in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 50.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 5, dated 1/14/14) as well as the revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) stamped by the MLIRB are enclosed.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No.: ZRHM-REXA-08-US
January 14, 2014
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in blue ink that reads 'Lynsey Hartman'.

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D.
Chairperson
KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 5) stamped by MLIRB
Approved revised recruitment material ("Philip Morris ZRHM-REXA-08-US Outbound Calls Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US CoRA Script v2 16-Dec-2013," "Philip Morris ZRHM-REXA-08-US Screening Appointment Confirmation Email v1 16-Dec-2013," Print ad, :30 radio script, Abbreviated online ad, Online ad, and the Abbreviated ads – Outdoor) stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures



January 30, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review of the following Spanish Translated document that is to be used at your site for the above-referenced protocol. A copy of the Spanish Translation Certificates was also received.

- "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Spanish)

I approved the "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Spanish) without modification and determined that the Informed Consent is in compliance with the U.S. Food and Drug Administration's regulations (21 CFR 50.25) and ICH Guidelines..

A copy of the approved "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Version 4, dated 1/30/14) stamped by MLIRB is enclosed.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D., Chairperson

KC/lh

enclosure: Approved "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Spanish)
stamped by MLIRB

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosure



April 14, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2" Amendment N°2 Version: Final 5.0, Date 14 April 2014, the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" for the above-referenced study.

I approved the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2" Amendment N°2 Version: Final 5.0, Date 14 April 2014, the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" without modification and determined that the revised Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 31.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 5, dated 04/14/14), the "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples" (Version 2, dated 04/14/14) as well as the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 2, dated 04/14/14) stamped by MLIRB are enclosed.



William Lewis, M.D.
Protocol No.: ZRHM-REXA-08-US
April 14, 2014
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in black ink that reads 'Lynsey Hartman'.

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D., Chairperson

KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation"
 (Version 5) stamped by MLIRB
 Approved revised "Informed Consent Document for Optional Long Term Storage (Bio-
 Banking) Of Urine, Plasma and Serum Samples" (Version 2) stamped by MLIRB
 Approved revised "Informed Consent Document for Genetic and Pharmacogenomic
 Analysis" (Version 2) stamped by MLIRB

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosures



April 14, 2014

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review on the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2," the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" for the above-referenced study.

I approved the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2," the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" without modification and determined that the revised Informed Consents are in compliance with the U.S. Food and Drug Administration's Informed Consent regulations (21 CFR 31.25) and ICH Guidelines.

Copies of the approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 6, dated 04/14/14), the "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples" (Version 3, dated 04/14/14) as well as the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 2, dated 04/14/14) stamped by MLIRB are enclosed.



H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Protocol No.: ZRHM-REXA-08-US
April 14, 2014
Page 2

Please do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely,

A handwritten signature in cursive script that reads 'Lynsey Hartman'.

Lynsey Hartman, CIM, IRB Coordinator
p.p. Kathy Chase, Pharm. D., Chairperson

KC/lh

enclosures: Approved revised "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 6) stamped by MLIRB
 Approved revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples" (Version 3) stamped by MLIRB
 Approved revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 2) stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosures



April 22, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."
Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis

As Chairperson of the MidLands Independent Review Board (MLIRB), I conducted Expedited Review of the following Spanish Translated documents that are to be used at your site for the above-referenced protocol. Copies of the Spanish Translation Certificates were also received.

- "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Spanish)
- "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Spanish)
- "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Spanish)
- Refer-A-Friend Program (English and Spanish)
- Demographics Form (Spanish)
- Participant Guide (Spanish)

I approved the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Spanish), "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Spanish), the "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Spanish), the Refer-A-Friend (English and Spanish), the Demographics Form (Spanish) as well as the Participant Guide (Spanish) without modification and determined that the Informed Consents are in compliance with the U.S. Food and Drug Administration's regulations (21 CFR 31.25).



William Lewis, M.D.
Protocol No. ZRHM-REXA-08-US
April 22, 2014
Page 2

Copies of the approved "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Spanish, Version 2, dated 04/22/14), the "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Spanish, Version 2, dated 04/22/14), the "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Version 2, dated 04/22/14), the Refer-A-Friend Program (Spanish and English), the Demographics Form, as well as the Participant Guide stamped by MLIRB are enclosed.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Lynsey Hartman, IRB Coordinator
p.p. Kathy Chase, Pharm. D., Chairperson

KC/lh

enclosures: Approved "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Spanish, Version 2) stamped by MLIRB
Approved "Informed Consent Document for Optional Long Term Storage (Bio-Banking) of Urine, Plasma and Serum Samples" (Spanish, Version 2) stamped by MLIRB
Approved "Authorization and Informed Consent to Participate in a Clinical Research [Study]" (Spanish, Version 2) stamped by MLIRB
Approved Demographic Form (Spanish) stamped by MLIRB
Approved Participant Guide (Spanish) stamped by MLIRB
Approved Refer-A-Friend (Spanish and English) stamped by MLIRB

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosures



April 28, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis

On April 14, 2014, the MidLands Independent Review Board (MLIRB), conducted Expedited Review on the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2," the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" for the above referenced protocol.

The last bullet point on page 17, of the "Informed Consent Authorization to Participate in a Clinical Investigation" was not revised to reflect the "240 ml" of water. This was in error. The revised bullet point should read as follows:

"You will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water"

The header revision requested on page 4 of the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" was revised incorrectly. This was in error. The revision should read as follows:

"Blood collection for transcriptomics (Day 0, Day 6 and Day 91)."

The above revisions were also made to the Spanish versions of the "Informed Consent Authorization to Participate in a Clinical Investigation" as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis."

Copies of the revised approved "Informed Consent Authorization to Participate in a Clinical Investigation" (Version 6, dated 04/28/14), the "Informed Consent Authorization to Participate in a Clinical Investigation" (Spanish) (Version 6, dated 04/28/14), the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 3, dated 04/28/14, as well as the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Spanish) (Version 3, dated 04/28/14) stamped by MLIRB are enclosed.



William Lewis, M.D.
Protocol No.: ZRHM-REXA-08-US
April 28, 2014
Page 2

Please place this letter in your study file.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

A handwritten signature in black ink that reads 'Lynsey Hartman'.

Lynsey Hartman, CIM
IRB Coordinator

/lh

enclosures: Revised approved "Informed Consent Authorization to Participate in a Clinical Investigation"
(Version 6) stamped by MLIRB
Revised approved "Informed Consent Document for Genetic and Pharmacogenomic Analysis"
(Version 3) stamped by MLIRB
Revised approved "Informed Consent Authorization to Participate in a Clinical Investigation"
(Spanish) (Version 6) stamped by MLIRB
Revised approved "Informed Consent Document for Genetic and Pharmacogenomic Analysis"
(Spanish) (Version 3) stamped by MLIRB

cc: Celisa Tolan, Covance Clinical Research Unit, Inc., w/enclosures



April 28, 2014

H. Frank Farmer, Jr., MD, PhD, FACP, CPI
Covance CRU Inc.
1900 Mason Ave., Ste 140
Daytona Beach, FL 32117

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Farmer:

On April 14, 2014, the MidLands Independent Review Board (MLIRB), conducted Expedited Review on the "Clinical Study Protocol ZRHM-REXA-08-US Amendment N°2," the revised Clinical Study Protocol, Version number: Final 5.0, Revision date: 14 April 2014, the revised "Informed Consent Authorization to Participate in a Clinical Investigation," the revised "Informed Consent Document for Optional Long Term Storage (Bio-Banking) Of Urine, Plasma and Serum Samples," as well as the revised "Informed Consent Document for Genetic and Pharmacogenomic Analysis" for the above referenced protocol.

The header revision requested on page 4 of the "Informed Consent Document for Genetic and Pharmacogenomic Analysis" was revised incorrectly. This was in error. The revision should read as follows:

"Blood collection for transcriptomics (Day 0, Day 6 and Day 91)."

A copy of the revised approved "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 3, dated 04/28/14) stamped by MLIRB is enclosed.

Please place this letter in your study file.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Lynsey Hartman, CIM
IRB Coordinator

/lh

enclosure: Revised approved "Informed Consent Document for Genetic and Pharmacogenomic Analysis" (Version 3) stamped by MLIRB

cc: Heather Camilo, Covance CRU Inc., w/enclosure



September 30, 2014

William Lewis, M.D.
Covance Clinical Research Unit Inc.
1341 W. Mockingbird Lane, Suite 400E
Dallas, TX 75247

Re: Clinical Study Protocol: ZRHM-REXA-08-US

"A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting."

Sponsor: Philip Morris Products S.A.

Dear Dr. Lewis

On April 22, 2014, the MidLands Independent Review Board (MLIRB), sent you an approval letter for the Spanish translated consents, for the above referenced study. The approval letter indicated the Spanish "Authorization and Informed Consent to Participate in a Clinical Research [Study]" version that was approved was (Version 2); however, this was in error. The reviewed and approved version of the Spanish "Authorization and Informed Consent to Participate in a Clinical Research [Study]" was Version 5.

Please place this letter in your study file.

We are apologize for any inconvenience this has caused.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

Lynsey Hartman, CIM
IRB Coordinator

/lh

cc: Celisa Tolan, Covance Clinical Research Unit, Inc.



16.1.3.17 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM APPROVAL LETTERS (LOCAL LANGUAGE)

Not applicable.



16.1.3.18 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM ENGLISH

There are 6 versions of the Subject Information and Informed Consent Form for the main study (1.0, 2.0, 3.0, 4.0, 5.0, and 6.0) for each site, 3 versions (1.0, 2.0, and 3.0) of the Genetic and Pharmacogenomic Analysis Informed Consent Form for each site, and 3 versions (1.0, 2.0, and 3.0) of the Optional Long Term Storage (Bio-banking) of Urine, Plasma and Serum Samples Informed Consent Form for Daytona Beach and 2 versions (1.0 and 2.0) for Dallas. All versions are presented in this section.



16.1.3.18.1 MAIN INFORMED CONSENT FORM

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.

**INTRODUCTION**

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.



A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.



Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis), There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 4 weeks (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.



You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and the spirometry test (a test to assess your lung function) have been performed.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, spirometry) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.



If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1, during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks and return to the site empty packs and unused THS Menthol tobacco sticks. During this visit no other assessments will take place.

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study not using any tobacco product and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 4 weeks before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period



- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles. You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.



Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse, urine pregnancy tests for women and urine cotinine test in male and female)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol breath test will be done (from a urine sample).



- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate).
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will participate in the study, you will be asked which product you would prefer to be randomized to, if you could choose your study arm. Please note, however, that your study arm will in fact be decided randomly. You cannot choose it.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be asked how you are feeling.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking



Questionnaire) and supplemental data on your smoking behavior.

- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
 - Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
- Spirometry will be done (Lung function test) without bronchodilator (has to be done prior to smoking).
- A sample of your urine will be taken for safety analysis.
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).



- Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
- Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of inflammation will be measured from the collected samples.
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking cessation if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three



blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.

2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
 - You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
 - Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
 - Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
 - Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
 - Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
 - Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).



Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

- You will be given support for smoking cessation if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Spirometry will be done (lung function test): without bronchodilator (must be done



prior to product use)

- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. You will be provided with nicotine replacement therapy if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and
Day 60 Visit (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay.



The following activities will take place during Day 30 and Day 60:

- Support for smoking cessation if needed (smoking abstinence arm only)
- You will be asked how you are feeling.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking cessation if needed (Arm 3 only)
- You will be asked how you are feeling
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.



- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- A pregnancy test (for female subjects)
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your needs during confinement stay.

Day 90

The following activities will take place during Day 90:

- Support for smoking cessation if needed (smoking abstinence arm only)
- You will be asked how you are feeling.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.



- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska “Stage of Change” questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

During this day the following procedures will take place:

- Support for smoking cessation if needed (smoking abstinence arm only)
- You will be asked how you are feeling.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Spirometry (Lung function test) without bronchodilator (has to be done prior to smoking). Spirometry will be done before you smoke or use the THS 2.2 Menthol



product.

- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff.
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.



During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 300 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal lavages that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.



The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate rooms. Arm 3 (smoking abstinence) will not be allowed in the smoking rooms.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted



- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- One day prior to the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visits.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation,



restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the investigational site.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.



To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,



- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

**COMPENSATION FOR BEING IN THIS STUDY**

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

**RIGHT TO WITHDRAW OR REMOVAL FROM STUDY**

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study,



such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Dallas Clinical Research Unit is 214-920-9053.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-



4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.



Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:
QC'd by _____
Date _____

APPROVED BY
JUL 02 2013
MLIRB
Multinational Independent Review Board

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1341 W. Mockingbird Ln., Ste 400E Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.



A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.



Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis). There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 4 weeks (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.



You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and the spirometry test (a test to assess your lung function) have been performed.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, spirometry) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.



If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1, during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks and return to the site empty packs and unused THS Menthol tobacco sticks. During this visit no other assessments will take place.

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study not using any tobacco product and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 4 weeks before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period



- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles. You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.



Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse, urine pregnancy tests for women and urine cotinine test in male and female)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol breath test will be done (from a urine sample).



- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females); As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will participate in the study, you will be asked which product you would prefer to be randomized to, if you could choose your study arm. Please note, however, that your study arm will in fact be decided randomly. You cannot choose it.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be asked how you are feeling.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking



Questionnaire) and supplemental data on your smoking behavior.

- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
 - Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
- Spirometry will be done (Lung function test) without bronchodilator (has to be done prior to smoking).
- A sample of your urine will be taken for safety analysis.
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).



- Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
- Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of inflammation will be measured from the collected samples.
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking cessation if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three



blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.

2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).



Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

- You will be given support for smoking cessation if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Spirometry will be done (lung function test): without bronchodilator (must be done



prior to product use)

- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth").will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. You will be provided with nicotine replacement therapy if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay.



The following activities will take place during Day 30 and Day 60:

- Support for smoking cessation if needed (smoking abstinence arm only)
- You will be asked how you are feeling.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking cessation if needed (Arm 3 only)
- You will be asked how you are feeling
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.



- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- A pregnancy test (for female subjects)
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your needs during confinement stay.

Day 90

The following activities will take place during Day 90:

- Support for smoking cessation if needed (smoking abstinence arm only)
- You will be asked how you are feeling.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.



- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

During this day the following procedures will take place:

- Support for smoking cessation if needed (smoking abstinence arm only)
- You will be asked how you are feeling.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Spirometry (Lung function test) without bronchodilator (has to be done prior to smoking). Spirometry will be done before you smoke or use the THS 2.2 Menthol



product.

- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff.
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.



During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 300 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal lavages that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.



The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate rooms. Arm 3 (smoking abstinence) will not be allowed in the smoking rooms.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted



- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- One day prior to the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visits.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation,



restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the investigational site.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.



To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,



- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

**COMPENSATION FOR BEING IN THIS STUDY**

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.



RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study,



such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Daytona Beach Clinical Research Unit is 386-366-6400.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-



4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time

APPROVED
JUL 02 2013
MLIRB
Menthol Research Laboratory
Informed Consent Review Board

I have received a signed and dated copy of this study consent form to keep._____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____



**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.



Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:
QC'd by _____
Date _____

APPROVED
JUL 02 2013
MLIRB
Independent Review Board

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	<u>Covance Dallas Site</u> Dr. William Lewis
Research Site Address:	<u>Covance Dallas Site</u> 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	<u>Covance Dallas Site</u> Ph: 214-920-9053
24 hour Telephone #:	<u>Covance Dallas Site</u> Ph: 972-955-5373
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.

**INTRODUCTION**

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different to smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red

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blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.



At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis), There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

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**STUDY DESIGN**

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00

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PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full lung function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic for Day 30 Visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Charger, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.

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- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles. You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.



You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of

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- abuse, urine pregnancy tests for women and urine cotinine test in male and female)
- You will be asked how you are feeling.
 - You will be asked about any medications that you are currently taking and your current medical status.
 - You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
 - You'll be asked about your smoking history.
 - An alcohol test will be done (from a urine sample or a breath test).
 - You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
 - A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
 - Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
 - Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
 - Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire.
 - You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
 - If you fulfill all eligibility criteria you will be enrolled in the study.
 - After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly and you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be

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performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.

- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide

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- levels in your blood) – (between 08:00 – 09:30 P.M.).
- Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
 - You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
 - Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
 - A sample of your urine will be taken for safety analysis.
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
 - Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
 - Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
 - Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of inflammation will be measured from the collected samples.
 - Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
 - All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On Day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).

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- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general

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urine test, and a urine pregnancy test for all women).

- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”) will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.



Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A Pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)

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- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover you stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water

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- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine

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- position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
 - Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
 - Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
 - End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
 - Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
 - You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
 - You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
 - Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have



any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 300 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal lavages that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from



commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate rooms. Arm 3 (smoking abstinence) will not be allowed in the smoking rooms.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-



containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.

- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will

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refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of

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ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will ‘open up’ the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you

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inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

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Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study

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- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

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**IN CASE OF INJURY**

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Dallas Clinical Research Unit is 214-920-9053.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

**CLOSING STATEMENT**

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

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AUTHORIZATION AND CONSENT TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

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Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:
QC'd by _____
Date _____

APPROVED BY

NOV 26 2013

MLIRB
Multinational Independent Review Board

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**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 13900 Mason Ave, Suite 140 Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.

**INTRODUCTION**

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different to smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red



blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.



At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis). There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).



STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00



PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full long function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic on Day 30 visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Calendar, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.



- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles. You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.



You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of



- abuse, urine pregnancy tests for women and urine cotinine test in male and female)
- You will be asked how you are feeling.
 - You will be asked about any medications that you are currently taking and your current medical status.
 - You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
 - You'll be asked about your smoking history.
 - An alcohol test will be done (from a urine sample or a breath test).
 - You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
 - A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
 - Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
 - Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
 - Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire.
 - You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
 - If you fulfill all eligibility criteria you will be enrolled in the study.
 - After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be

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performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.

- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide

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- levels in your blood) – (between 08:00 – 09:30 P.M.).
- Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
 - You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
 - Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
 - A sample of your urine will be taken for safety analysis.
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
 - Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
 - Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
 - Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of inflammation will be measured from the collected samples.
 - Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
 - All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).



- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general

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urine test, and a urine pregnancy test for all women).

- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.



Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will be have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)



- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover your stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water



- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine

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position prior to measurement)

- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk makers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have



any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 300 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal lavages that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from



commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate rooms. Arm 3 (smoking abstinence) will not be allowed in the smoking rooms.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-



- containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
 - Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
 - Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
 - Consumption of water is also allowed without any restriction.
 - A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will



refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of



ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you

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inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00



Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare

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- or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

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**IN CASE OF INJURY**

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Daytona Beach Clinical Research Unit is 386-366-6400.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

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**CLOSING STATEMENT**

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.



Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:

QC'd by _____

Date _____

Draft/Date: 19 Nov 2013

Version No. 2

Approved by MLIRB on 11/26/13

Protocol#: ZRHM-REXA-08-US

APPROVED BY
NOV 26 2013
MLIRB
Multinational Independent Review Board

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different to smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red

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blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.



At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis). There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

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**STUDY DESIGN**

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the

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study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full lung function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic for Day 30 Visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Charger, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.

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- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must

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be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

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If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire.
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly and you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will

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provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols (“cholesterols”) in your blood (has to be done

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- at least in 10-hours fasting condition).
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (prior to full lung function test).
 - Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
 - Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
 - Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
 - A sample of your urine will be taken for safety analysis.
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
 - Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
 - Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
 - Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of

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inflammation will be measured from the collected samples.

- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On Day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be

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performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).

- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

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- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on

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THS 2.2 Menthol will be given

- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

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The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A Pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)

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- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover your stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted

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only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.

- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska “Stage of Change” questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)

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- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal lavages that will be analyzed by an appropriately equipped laboratory. The designated

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analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

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If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is

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among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

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If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

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**RISKS TO THE UNBORN**

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be **hazardous**. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking

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**COST**

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more

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than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

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A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Dallas Clinical Research Unit is 214-920-9053.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

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**PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS**

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

**PRIMARY CARE DOCTOR NOTIFICATION**

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

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Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

APPROVED BY

DEC 13 2013

Printed Name of the Person Obtaining the
Authorization

MLIRB
Midlands Independent Review Board

To be Completed by Covance Staff Only:

QC'd by _____

Date _____

Date: 11 Dec 2013

Version No. 3

Approved by MLIRB on 12/13/13

Protocol#: ZRHM-REXA-08-US

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 13900 Mason Ave, Suite 140 Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS. 2.2 Menthol use are different to smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red



blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.



At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis). There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

**STUDY DESIGN**

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the



study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full long function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic on Day 30 visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Calendar, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.



- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to



three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the

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investigational site.

If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate).
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers

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which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).

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- Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
- A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
- Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
- A sample of your urine will be taken for safety analysis.
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
- Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in



a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of inflammation will be measured from the collected samples.

- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.



- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function test will be done (spirometry with bronchodilator, and tow other techniques using the spirometer). All the assessments have to be done prior to product use.



- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay



at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

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During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover your stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:



- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk makers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to

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evaluate signs and symptoms of withdrawal)

- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal

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lavages that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.



- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

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Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce

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certain measures to limit them. During the course of the study, a team of trained investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.



RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up

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smoking

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security



number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot



be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Daytona Beach Clinical Research Unit is 386-366-6400.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by



the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

**PRIMARY CARE DOCTOR NOTIFICATION**

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.



Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

APPROVED BY
DEC 13 2013
MLIRB
National Independent Review Board

To be Completed by Covance Staff Only:

QC'd by _____

Date _____

Date: 11 Dec 2013

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**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	<u>Covance Dallas Site</u> Dr. William Lewis
Research Site Address:	<u>Covance Dallas Site</u> 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	<u>Covance Dallas Site</u> Ph: 214-920-9053
24 hour Telephone #:	<u>Covance Dallas Site</u> Ph: 972-955-5373
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different than smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

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A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

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RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female over the age of 22 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are seriously thinking about quitting smoking within the next 6 months, then you are not eligible to participate in this study. However, you must be willing to abstain from smoking for the duration of the study if you are randomly selected for the smoking abstinence arm.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study

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you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

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During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full lung function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic for Day 30 Visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Charger, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)

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- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

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If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

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- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire.
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly and you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

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- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide

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- levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
 - Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
 - Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
 - A sample of your urine will be taken for safety analysis.
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
 - Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
 - Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
 - Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
 - All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

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- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On Day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette

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Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.

- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests

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(hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).

- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth")_will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects

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will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/ regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A Pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood

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- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

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Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover you stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water

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- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska “Stage of Change” questionnaire).
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index

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- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site.

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Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood and Urine Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to

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this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-

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containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.

- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you may need to let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a

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medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

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ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

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If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00

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Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

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The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**WHO IS ORGANIZING THE RESEARCH?**

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Dallas Clinical Research Unit is 214-920-9053.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your



participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood and urine samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date: 13 Jan 2014 _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

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Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:

QC'd by _____

Date _____

Date: 13 Jan 2014

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APPROVED BY
JAN 14 2014
MLIRB
Multinational Independent Review Board

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1900 Mason Ave, Suite 140 Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.

**INTRODUCTION**

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

Cigarette smoking causes cancer, lung and heart disease and several other serious diseases. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS. 2.2 Menthol use are different to smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red

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blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.



At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

Smoking is addictive and causes serious, fatal diseases such as lung cancer, cardiovascular disease (heart disease), chronic obstructive lung diseases (emphysema and bronchitis). There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female between the ages of 22 and 65 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).



STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the

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study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full long function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic on Day 30 visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Calendar, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.



- You will be asked questions about your smoking history
- You will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to



three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the

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investigational site.

If you are eligible,

- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate).
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are willing to quit smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers

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which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).

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- Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
- A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
- Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
- A sample of your urine will be taken for safety analysis.
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
- Nasal lavages. During the procedure, you will be asked to position your head forward. This collection involves flushing out the nose (nostrils) with salt water (saline). It is done using a tool called nasal olive, rubber tubing and about a teaspoon (5 ml) of pre-warmed saline solution. The teaspoon of salt water solution is slowly ejected through the nostrils in order to wash the nasal cavity. The solution is then left to dwell in the nostril for 30 seconds, after which the fluid is withdrawn back into the syringe. The fluid will be flushed back into the nasal cavity 20 times in



a 1 minute period (1 repeated flush and withdrawal every 3 seconds). Markers of inflammation will be measured from the collected samples.

- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.



- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional inform consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function test will be done (spirometry with bronchodilator, and tow other techniques using the spirometer). All the assessments have to be done prior to product use.



- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay



at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

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During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Day 31 and Day 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover your stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:



- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal lavages collection (flushing out the nose (nostrils) with salt water)
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked to fill out a specific questionnaire about your intention to quit smoking (Prochaska “Stage of Change” questionnaire)
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A general urine test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk makers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to

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evaluate signs and symptoms of withdrawal)

- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood, Urine and Nasal Lavage Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol and inflammatory cytokines in nasal

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lavages that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers, and nasal lavage sampling will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.



- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers.

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Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce

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certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

**RISKS TO THE UNBORN**

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up

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smoking

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security



number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot



be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Daytona Beach Clinical Research Unit is 386-366-6400.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by



the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

**PRIMARY CARE DOCTOR NOTIFICATION**

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood, urine, and nasal lavage samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.



Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:
QC'd by _____
Date _____

APPROVED BY

DEC 26 2013

MLIRB
Multi-Local Institutional Review Board

Date: 11 Dec 2013
Version No. 4
Approved by MLIRB on 12/26/13
Protocol#: ZRHM-REXA-08-US

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	<u>Covance Dallas Site</u> Dr. William Lewis
Research Site Address:	<u>Covance Dallas Site</u> 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	<u>Covance Dallas Site</u> Ph: 214-920-9053
24 hour Telephone #:	<u>Covance Dallas Site</u> Ph: 972-955-5373
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different than smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

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A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

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RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female over the age of 22 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are seriously thinking about quitting smoking within the next 6 months, then you are not eligible to participate in this study. However, you must be willing to abstain from smoking for the duration of the study if you are randomly selected for the smoking abstinence arm.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study

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you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.

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During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full lung function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic for Day 30 Visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Charger, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)

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- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

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If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

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- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire.
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly and you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

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- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide

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- levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
 - Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
 - Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
 - A sample of your urine will be taken for safety analysis.
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
 - Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
 - Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
 - Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
 - All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

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- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On Day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the evening between 08:00 – 09:30 P.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 A.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette

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Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.

- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests

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(hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).

- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”) will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects

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will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and
Day 60 Visit (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A urine pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood

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- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

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Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover you stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty or unused packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water

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- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska “Stage of Change” questionnaire).
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period

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- A urine safety test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the

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lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood and Urine Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

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Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.

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- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you may need to let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect

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your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare,

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localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable/transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as

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women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00

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Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time.

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If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

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**WHO IS ORGANIZING THE RESEARCH?**

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Dallas Clinical Research Unit is 214-920-9053.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

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You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood and urine samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

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Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:
QC'd by _____
Date _____

APPROVED BY
APR 14 2014
MLIRB
Independent Review Board

Date: 14 Apr 2014

Version No. 5

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1900 Mason Ave, Suite 140 Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different than smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.



A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

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RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female over the age of 22 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are seriously thinking about quitting smoking within the next 6 months, then you are not eligible to participate in this study. However, you must be willing to abstain from smoking for the duration of the study if you are randomly selected for the smoking abstinence arm.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3

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study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.



During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full long function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic on Day 30 visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Calendar, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)



- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.



If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

If you are eligible,

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- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate).
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

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- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).

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- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
- A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
- Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
- A sample of your urine will be taken for safety analysis.
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement.
- Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the morning between 08:00 – 09:30 A.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to



complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 P.M.) (Day 1 to Day 5).

- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be



kept for long term bio-storage and further analysis if consent was given for this procedure.

- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

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Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and Day 60 Visit (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will be have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A pregnancy test (for female subjects)

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- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)



- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover your stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after Cough and Minnesota Nicotine Withdrawal Scale questionnaires, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will



then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection

- You will take a tablet of caffeine approximately 200 mg with approximately 200 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology,

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- clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
 - A general urine test, and a urine pregnancy test for all women
 - Physical examination including weight, waist circumference and body mass index
 - Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
 - You will have an electrocardiogram - a painless heart rhythm tracing.
 - Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
 - Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
 - End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
 - Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk makers will be analyzed.
 - You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
 - You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
 - Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

**Withdrawal Procedures**

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood and Urine Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law.

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regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.



- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.



If you have private medical insurance you may need to let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.



STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will 'open up' the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be **hazardous**. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

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Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00

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Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of

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benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing



confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Daytona Beach Clinical Research Unit is 386-366-6400.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.



You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood and urine samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

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Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:
QC'd by _____
Date _____

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APPROVED BY
JAN 14 2014
MLIRB
Medical Research Ethics Board

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different than smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.

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A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.

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RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female over the age of 22 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are seriously thinking about quitting smoking within the next 6 months, then you are not eligible to participate in this study. However, you must be willing to abstain from smoking for the duration of the study if you are randomly selected for the smoking abstinence arm.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study

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you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3 study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.



During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full lung function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic for Day 30 Visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Charger, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)

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- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.

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If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

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- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate)..
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire.
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly and you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

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- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide

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- levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
 - A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
 - Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
 - Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
 - A sample of your urine will be taken for safety analysis.
 - Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
 - Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
 - Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
 - You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
 - Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
 - All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

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- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On Day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the evening between 08:00 – 09:30 P.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 A.M.) (Day 1 to Day 5).
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette

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Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.

- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Blood and urine samples will be collected in order to perform laboratory tests

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(hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).

- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects

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will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A urine pregnancy test (for female subjects)
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood

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- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

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Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover you stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty or unused packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water

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- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska “Stage of Change” questionnaire).
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period

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- A urine safety test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk markers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you may be asked to complete the

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lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood and Urine Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

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Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.
- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.

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- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you may need to let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect

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your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare,

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localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will ‘open up’ the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part to this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception
 - condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as

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women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00

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Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time.

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If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

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**WHO IS ORGANIZING THE RESEARCH?**

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Dallas Clinical Research Unit is 214-920-9053.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

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You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES**

Please read the following paragraph out loud to the person obtaining the consent.

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood and urine samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy

Signature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a signed and dated copy of this study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

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**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

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Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

APPROVED BY

APR 28 2014

MLIRB
Millers Independent Review Board

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:

QC'd by _____

Date _____

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**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	<u>Covance Daytona Beach Site</u> Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	<u>Covance Daytona Beach Site</u> 1900 Mason Ave, Suite 140 Daytona Beach, FL 32117
Telephone #:	<u>Covance Daytona Beach Site</u> Ph: 386-366-6400
24 hour Telephone #:	<u>Covance Daytona Beach Site</u> Ph: 386-366-6400
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

You are invited to participate in a research study. However, before you give your consent to be a study participant, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve. You will be given a copy of this informed consent form to take home with you.



INTRODUCTION

Your participation in this research study is voluntary. It is important that you read and understand the following explanation of the proposed procedures. This informed consent form describes the purpose, procedures, benefits, alternatives, recognized or known risks, discomforts, and precautions of the study including the duration and nature of your participation. It also describes your right to withdraw from the study at any time. To enter the study, you, as the research participant, must sign and date this informed consent form.

Please Note: If you are not completely truthful with your doctor regarding your health history, including allergies and medication usage, you may be harmed by participating in this study.

NATURE AND PURPOSE OF THE STUDY

The Sponsor of this study is Philip Morris Products, a manufacturer of tobacco products. The Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

The Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) is an investigational product being developed as an alternative to conventional cigarettes that has not been approved by the US Food and Drug Administration (FDA).

It is thought that by heating tobacco, rather than burning it as in a conventional cigarette, it may be possible to reduce the harmful effects of smoking.

THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different than smoking normal cigarettes.

The overall purpose of this study is to collect information about the use of the investigational product THS 2.2 Menthol when given to research subjects who are in confinement at the research site and then in ambulatory setting. The research study will compare the use of the THS 2.2 Menthol product to menthol conventional cigarettes, and smoking abstinence. During this study several biomarkers of exposure in the body and risk markers will be measured. The study will also obtain safety information related to the use of the THS 2.2 Menthol product.

Biomarkers of exposure are substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you intake carbon monoxide when you smoke. Carbon monoxide binds to certain parts of your red blood cells called hemoglobin. Carbon monoxide can replace oxygen in your red blood cell. The level of carbon monoxide bound to hemoglobin will be measured in this study and is referred to as biomarker of exposure to carbon monoxide.



A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection. To better understand the biological (physiological) differences between the THS 2.2 Menthol product, menthol conventional cigarettes and smoking abstinence, other measurements will be taken, including markers of irritation (inflammation) in the nose and of types of cholesterol in the blood.

Additional goals of this research study are to better understand, what the body does to nicotine and its break-down products (including the enzymes involved in the break-down) in smokers switching from menthol conventional cigarettes to THS 2.2 Menthol as compared to smokers continuing to smoke conventional menthol cigarettes. This study will also evaluate smoking patterns and preferences (i.e., smoking topography), product use and related subjective effects.

This study is for research purposes only and is not intended to treat any medical condition.

You will also be invited to participate in two additional, optional sub-studies. One will involve pharmacogenomics analysis of your biological samples. You are not required to participate in either of these two optional sub-studies. You will be given 2 separate informed consent forms for these additional sub-studies. **If you do not wish to participate in these additional sub-studies, your participation in this main research study will not be affected.**

Covance Clinical Research Unit Inc. is paid to test the investigational THS 2.2 Menthol product. The study doctors in this study work for Covance, but do not have a financial interest in the outcome of this study.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being developed by the Sponsor, and evaluated in this study, is called THS 2.2 Menthol. With this product, the heating of the tobacco is maintained at a temperature much lower than what is observed for normal (conventional) cigarettes. The THS 2.2 Menthol product consists of the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable.

The Tobacco Heating Device comprises everything in THS 2.2 Menthol product except the Menthol Tobacco Stick itself. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick). Unlike normal cigarettes, Menthol Tobacco Sticks do not burn down during their consumption and their length remains constant after use.

At this time you need to understand that THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different from smoking normal cigarettes.



RESEARCH PARTICIPANT SELECTION

You are invited to participate in this study because you are apparently a healthy smoking male or female over the age of 22 years old and you smoke menthol conventional cigarettes and may be suitable to participate in this study.

If you are seriously thinking about quitting smoking within the next 6 months, then you are not eligible to participate in this study. However, you must be willing to abstain from smoking for the duration of the study if you are randomly selected for the smoking abstinence arm.

If you are female you must not be pregnant or nursing. If you decide to participate in this study, you will be asked to use appropriate forms of birth control during the study.

It is important that you answer all of the screening questions truthfully and completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs. **It could be dangerous to your health if you do not completely disclose all information about your medical history, any medical condition you have and any medication that you have taken.**

160 participants will be randomized in this multi-site research study.

STUDY DURATION

The duration of your participation in this study is approximately 123 to 150 days including the screening period. A screening visit will take place up to 28 days (Day -30 to Day -3) prior to the admission to the investigational site (to determine if you qualify in this research study). This study requires confinement of 9 days/ 8 nights (Day -2 to Day 6) at the investigational site followed by 3 visits on Days 30-31, 60-61 and 90-91. Each visit will cover 2 consecutive days (with 1 overnight stay at each visit) on site. For the Day 30 Visit, you will check-in prior 08:30AM and will check-out after all assessments are done on Day 31. For Day 60 Visit, you will check-in prior 08:30AM on Day 60, and will check-out after all assessments are done on Day 61. For Day 90 Visit, you will check-in prior 08:30AM on Day 90, and will be discharged on Day 91 after all assessments are done.

After the Day 91, there will be a 28-day safety follow up period during which you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period that has not been resolved following discharge from the site on Day 91.

During the study, from screening until the end of the safety follow up period, you should always contact the site before you take any medication (prescribed or over the counter).

STUDY DESIGN

This research study will be an "open label study". This means that you, the study doctor and the Sponsor will know which products you are given. Once you qualify for the study you will be randomized (assigned by chance like flipping a coin) to 1 of the following 3

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study arms. This will take place on Day 0. You will be informed about the arm you are assigned to on Day 1. You will not have a choice as to which arm you are assigned.

You will have 50% chance of being included in Arm 1 and 25% in either Arm 2 or 3.

- **Arm# 1** Tobacco Heating System, THS 2.2 Menthol Arm (80 participants).
- **Arm# 2** Menthol conventional cigarettes Arm (40 participants).
- **Arm# 3** Smoking abstinence Arm (40 participants).

If you are assigned to Arm 1 or 2, smoking during the confinement period (from Day 1 until the time you are discharged from the site on Day 6) will be allowed between 06:30 AM and 11:00 PM each day. During this time, you can use as many THS 2.2 Menthol tobacco sticks as you want if you are in Arm 1 or smoke as many menthol conventional cigarettes as you want if you are in Arm 2. You will not have free access to your menthol conventional cigarettes or the THS 2.2 Menthol product. The study staff will distribute the menthol conventional cigarettes and the THS 2.2 Menthol tobacco sticks when requested by you one by one. Smoking is not allowed during the conduct of the study procedures. At Day 6 you will not be able to smoke or use the THS 2.2 Menthol product before all laboratory tests and all tests to assess your full lung functions have been performed. For this study, outdoor smoking is not allowed so you will be required to smoke your menthol conventional cigarettes or use the THS 2.2 Menthol product in an indoor smoking booth. The booth is made of glass and holds approximately 8 people at a time. The booth uses filters to contain the smoke and keep it from exiting the booth. A staff member will advise you on using the booths and how to put out your menthol conventional cigarettes or dispose the THS 2.2 Menthol tobacco sticks when you are finished smoking or using the THS 2.2 Menthol product.

If you are assigned to Arm 3, complete smoking abstinence (SA) is required throughout the study from Day 1 until Day 91. During confinement period from Day 1 to Day 6 all research participants in Arm 3 will be closely monitored by the site staff for possible signs and symptoms of nicotine withdrawal. During this time, you are not allowed to take medication to support smoking abstinence or use any tobacco/nicotine containing product. You will be provided with psychological support during the period of smoking abstinence.

At the end of the confinement period when you are discharged from the site on Day 6, you will be instructed to continue your assigned product/regimen in an ambulatory setting for 86 days, i.e. keep using THS 2.2 Menthol if you are assigned to Arm 1 and keep smoking your menthol conventional cigarettes if you are assigned to Arm 2, or abstain from smoking if you are assigned to Arm 3. You will need to record daily in an electronic diary any use of THS 2.2 Menthol product, conventional cigarettes (menthol or non-menthol), Nicotine Replacement Therapy, e.g. nicotine gum, or other nicotine/tobacco-containing products. You will not be asked to stop participating in the study if you use any other nicotine/tobacco-containing products other than the assigned product/regimen during the ambulatory period.



During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from your check-in in the morning prior to 08:30AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after some assessments (e.g. Minnesota Nicotine Withdrawal Scale and cough questionnaires, full long function assessments) have been performed until time of discharge of Day 91. If you have been assigned to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

If you have been assigned to THS 2.2 Menthol arm, you will be instructed by the site staff how to safely dispose the used THS Menthol Tobacco sticks.

If you are assigned to Arm 1 (THS 2.2 Menthol arm), during the ambulatory period, you will need to visit the site approximately every 2 weeks in order to be supplied with new packs of THS 2.2 Menthol Tobacco Sticks. During this visit no other assessments will take place. When you come to the clinic on Day 30 visit, Day 60 Visit, and Day 90 Visit you should return to the site empty packs, unused packs, and opened packs with unused THS Menthol tobacco sticks as well as THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Calendar, THS accessories).

If at any time during the study you wish to quit smoking, the study staff will support you with this decision and you will be referred to medical services. You will remain in the study and complete all remaining visits and procedures. However at any time you may decide to withdraw from the study completely.

SCREENING

You will come to the clinic for a screening visit to determine if you are eligible to participate in this study. The Screening visit will take place up to 28 days before admission to the site. You will be expected to arrive at the investigational site having fasted for at least 10 hours, which is required for certain blood tests. Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The following tests and procedures will be performed to determine if you qualify to take part in this study:

- You will be given advice on the risk of smoking (brief interview according to U.S. Public Health Service recommendations)/smoking cessation advice and debriefing on the THS 2.2 Menthol product.
- Your demographic information will be collected (age, sex, race, ethnicity).
- You will be asked about your medical history and current medical status.
- You will be asked about any medications you have taken in the past and any medications that you are currently taking. You will be told which medications you will be allowed to take while you are in the study.
- You will be asked how you are feeling.
- You will be asked questions about your smoking history
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire)

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- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- You will be asked what brand of normal menthol cigarettes you smoke.
- You will have a physical examination, measurement of vital signs (pulse, blood pressure respiratory rate at least 5 minutes in supine position prior to measurement, respiratory rate), and measurements of height and weight to calculate your body mass index (BMI),
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing). An ECG shows the pattern of your heart beat. Males subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects will not be allowed to wear a bra.
- Blood and urine samples for clinical laboratory testing will be obtained – after 10 hours of fasting period
- A urine pregnancy test will also be performed on all women.
- A screening for HIV (aids) and hepatitis (from a blood sample), drugs of abuse (from a urine sample), cotinine (from a urine sample) and alcohol (from a urine sample or from a breath test)) will be done
- A demonstration of the THS 2.2 Menthol will be performed by the site staff during this visit.
- An X-ray will be performed on your chest if one was not already performed within the past 6 months. The X-ray will take place at a radiology (X-ray) unit. The chest X-ray examination consists of two X-ray images taken at different angles.
- You will be asked to blow into a machine called a Spirometer. This will be done before and after inhaling a short-acting bronchodilator (drug that will 'open up' the lungs). This machine will measure how well your lungs are functioning. This test will be done at least one hour after smoking
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).
- You will be given two additional optional informed consents forms for optional sub-studies. Your participation in the main study does not depend on your decision to sign or not sign these informed consent forms.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state.



If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that the HIV testing will not be completed.

You will be told to continue smoking your preferred brand of menthol conventional cigarettes.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments performed both at screening and at admission day (Day -2) are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from screening which indicates a change to your health or physical being which may make you ineligible at check in.

If, following the completion of screening procedures, you are qualified for the study you will need to purchase your own preferred single brand of menthol conventional cigarettes prior to Admission. On Day -2, you will need to give to the study staff the number of packs that you think you might smoke in 9 days plus 4 extra packs. The menthol conventional cigarettes will not be provided by the Sponsor. Any unused/partially used packs will be returned to you when you are discharged from the site.

STUDY PROCEDURES

Periodically during the study, vital signs (blood pressure, pulse) will be measured and ECGs will be performed. You will also be asked about how you are feeling and if you have taken any medications. In addition, the blood and/or urine samples collected in this study may be used for routine clinical laboratory testing, study drug analysis, selected smoke constituents, biomarkers, risk markers, nicotine levels and carbon monoxide. You will also be asked to fill out several questionnaires about cigarettes, smoking, smoking preference, your perception of risks associated with using THS 2.2 Menthol product and smoking abstinence. Please see below the list of assessments that you need to perform each day.

Based on the study design, you may be selected as an alternate for this study. In this case you may follow the procedures of Admission and Baseline (Day -1 and Day 0), but will not be assigned to any study arm and you will not take part in the rest of the study.

Day -2 (Admission/Check-in)

You will come to the research center on Day-2 to begin your confinement at the investigational site.

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- A physical examination will be performed and your weight and waist will be measured. Your body mass index will be calculated.
- Urine samples will be collected in order to perform laboratory tests (test for drug of abuse and a urine pregnancy tests for women)
- You will be asked how you are feeling.
- You will be asked about any medications that you are currently taking and your current medical status.
- You will receive information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol.
- You'll be asked about your smoking history.
- An alcohol test will be done (from a urine sample or a breath test).
- You will be asked if you are ready to comply with the procedures described in the study protocol (e.g. if you are ready to abstain from smoking for up to 91 days)
- A Carbon monoxide breath test will be done (measurement of the amount of carbon monoxide in the breath).
- Vital signs will be taken (blood pressure, pulse rate, respiratory rate).
- Your current menthol conventional cigarette brand will be identified (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff. They will take a photo of your pack).
- Before product trial of THS 2.2 Menthol, you will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska "Stage of Change" questionnaire).
- You will have a trial of THS 2.2 Menthol product (only after the pregnancy test is confirmed negative in females): As the last procedure of the eligibility criteria you will try THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). You will then be asked if you are ready to use the THS 2.2 Menthol product during the duration of the study, if you are randomly assigned to Arm 1.
- If you fulfill all eligibility criteria you will be enrolled in the study.
- After the confirmation that you will be enrolled, you will be asked which product you would prefer to be randomized to, if you could choose your study arm (Product preference questions). Please note, however, that your study arm will in fact be decided randomly you cannot choose it. If your preference is to be randomized on the SA arm, you will be asked again to complete the Prochaska 'Stage of Change' questionnaire. Based on your reply you may be withdrawn from the study.

You will continue to smoke your own menthol conventional cigarettes until 11:00 PM.

Baseline Day -1

- From 10:00 A.M. and until 2:00 P.M. you will urinate into disposable containers which will then be handed over to the personnel of the Site. Site personnel will provide detailed information concerning the method of urine collection. From the collected urine, biomarkers of exposure and risk markers will be analyzed.

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- You will be asked how you are feeling and about any medications that you are currently taking.
- Carbon monoxide breath testing will be done four times per day; the first test will be performed 15 minutes prior to the first smoking event the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Vital signs will be measured (blood pressure, heart rate, respiratory rate).
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the THS 2.2 Menthol product and the menthol conventional cigarettes.
- You will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- A blood sample will be taken to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30PM).
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Baseline Day 0

You will be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- Start of the 24-hour urine collection of Day 0 (each time you will urinate into disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- You will be asked how you are feeling and about any medications that you are currently taking.
- A carbon monoxide breath test will be done (four times per day; the first test will be performed 15 minutes prior to the first smoking event; the other tests will be done between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00-09:30 P.M.
- Blood samples for Day 0 will be collected as follows:
 - Sample for hematology and clinical chemistry and risk markers - to be taken after at least 10 hours of fasting.
 - Sample of blood for long term bio-storage of serum and plasma for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition).
 - Sample for bio-storage for further analysis of transcriptomics (if you gave consent for genetic testing sample) (has to be done at least in 10-hours fasting condition).
 - Sample to measure oxysterols ("cholesterols") in your blood (has to be done at least in 10-hours fasting condition).

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- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (prior to full lung function test).
- Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking).
- A sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine) (between 04:00 – 05:30 P.M.) 6 hours after the intake of caffeine tablet.
- Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 08:00 – 09:30 P.M.).
- Sample to measure the nicotine and cotinine levels in your blood (between 08:00 – 09:30 P.M.).
- You will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water (to measure CYP1A2) (between 10:00 – 11:30 A.M.).
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to smoking.
- A sample of your urine will be taken for safety analysis.
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Human smoking topography (a painless procedure to assess your smoking behavior) will be conducted only if you are provided with the HST SODIM® device (a device that measures a person's unique way of smoking). Please note that the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals between 08:00-11:00 P.M.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal). The questionnaires have to be done prior to smoking, but no later than 10:00 A.M.
- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M.
- Nasal Epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth"), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more details if you sign the informed consent form for these procedures.
- All smoked menthol conventional cigarette butts will be collected for accountability.

Exposure period Day 1 to Day 5

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be notified about which study arm you have been randomly assigned to prior to 06:30 A.M of Day 1.
- You will be given support for smoking abstinence if needed (SA arm only).
- 24-hour urine collection will take place from the morning of Day 1 until the morning of Day 6 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection.
- On day 1 it is the end of 24-hour urine collection that started on Day 0. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- From the collected urine over the 24 hours on Days 2, 3, 4, and 5 biomarkers of exposure and creatinine will be analyzed.
- You will be asked how you are feeling and about any medications that you are currently taking.
- Blood samples will be collected as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30 P.M. each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 08:00 – 09:30 A.M. for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00 – 01:30 P.M., 04:00 – 05:30 P.M., and 08:00 – 09:30 P.M. for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 08:00 – 09:30PM each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomized to smoking abstinence, one blood sample in the evening between 08:00 – 09:30 P.M.
- On Day 5 only, a blood sample will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): The sample will be collected between 04:00 – 05:30 P.M., 6 hours after the intake of caffeine tablet.
- You will have a carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to your first cigarette or product use and between 08:00 – 09:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00 – 01:30 P.M., 04:00 – 05:30PM, and 08:00 – 09:30 P.M. for all subjects (Day 1 to Day 5).
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate: (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to



complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00 A.M.) (Day 1 to Day 5).

- You will be asked to fill a questionnaire to evaluate the product (Modified Cigarette Evaluation Questionnaire) and one questionnaire to evaluate your desire to smoke (Questionnaire of Smoking Urges) between 08:00 – 11:00 P.M. from Day 1 to Day 5.
- Only on Day 4 you will be asked to complete a questionnaire on your socioeconomic status. You will be asked a series of questions related to your education, occupational status, size and annual income of your household. You can answer as many questions as you feel comfortable answering.
- Only on Day 4 you will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- Only on Day 5 you will be asked to complete two questionnaires to assess your current and past smoking behavior (Behavioral Risk Factor Questionnaire and Smoking Questionnaire) and supplemental data on your smoking behavior.
- Only on Day 5, you will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water (to measure CYP1A2) (between 10:00–11:30 A.M.).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4).

Smoking of menthol conventional cigarettes or use of the THS 2.2 Menthol product is allowed from 06:30 A.M. until 11:00 P.M., but not during the study procedures. Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, you will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Day 6 (Discharge)

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

- You will be given support for smoking abstinence if needed (Arm 3 only).
- Blood samples will be collected (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For the smoking abstinence arm one blood sample will be taken between 08:00 – 09:30 A.M.).
- On Day 6 it is the end of 24-hour urine collection that started on Day 5. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed a mutagenicity test will be done. Urine samples will be

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kept for long term bio-storage and further analysis if consent was given for this procedure.

- Blood and urine samples will be collected in order to perform laboratory tests (hematology, clinical chemistry – after at least 10 hours fasting period), a general urine test, and a urine pregnancy test for all women).
- Blood samples will be collected for risk marker analysis- to be taken after least 10 hours of fasting.
- Blood samples will be collected for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period-, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures.
- A blood sample will be collected to measure oxysterols (after at least 10 hours of fasting period).
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- A blood sample will be collected to measure CYP2A6 activity (must be done prior to smoking).
- Physical examination will be performed including weight and body mass index
- You will complete a questionnaire of Assessment of Cough (a questionnaire assessing your cough) and a Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal) (must be done prior to product use, but no later than 10:00 A.M.)
- Full lung function test will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.
- A Carbon monoxide breath test will be done
- Vital signs will be measured (blood pressure, pulse rate, respiratory rate)
- An electrocardiogram will be done (, a painless tracing of your heart rate & rhythm)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol will be given
- You will be asked how you are feeling and about any medications that you are currently taking.
- Nasal epithelial collection ("collections of the cells from the nose") and buccal sample collection ("collection of the cells from the mouth") will take place, only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- You will be discharged from the site

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Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff.

Prior to discharge from the site you will be given an electronic diary, that you will use to record any use of THS 2.2 Menthol Tobacco Sticks, conventional cigarettes (menthol and non-menthol), nicotine replacement therapy products, or the use of other nicotine/tobacco containing products. All research participants including Arm 3 must complete this diary on a daily basis from the time of Discharge on Day 6 until the time of discharge on Day 91. You will be trained in the use of this electronic diary.

After the time of discharge on Day 6, you will be instructed to continue your assigned product/regimen at home for 86 days. If you are allocated to the SA arm, you may be provided with nicotine replacement therapy (no other medicinal product supportive for smoking cessation will be allowed) if considered necessary by the Investigator or requested by you.

Day 30 Visit (from check in prior 08:30 A.M. on Day 30 to check-out on Day 31) and **Day 60 Visit** (from check in prior 08:30 A.M. to check out on Day 61)

Smoking or product use will be allowed on site from your check in to around 11:00PM on Day 30 and Day 60 and from 06:30AM on Day 31 and Day 61. There is no restriction for smoking / product use prior you check in at site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product. During Day 30 visit and Day 60 Visit you will be asked to continue completing your e-diary on a daily basis.

You will be asked to bring enough supplies of the product you have been using to cover your confinement stay. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic. If you are assigned to THS 2.2 arm, you will be have to bring all unused packs, empty packs and unused THS Menthol Tobacco Sticks. You will also have to bring the THS 2.2 Device (including all parts – holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and your e-diary.

The following activities will take place during Day 30 and Day 60:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications you are currently taking.
- 24-hour urine collection will take place from the morning of Day 30 and 60, until the morning of Day 31 and 61 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- A urine pregnancy test (for female subjects)

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- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Physical examination including weight, and calculation of body mass index
- You will have an ECG (electrocardiogram - a painless heart rhythm tracing)
- You will have a carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska “Stage of Change” questionnaire).
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 31 and Day 61

During these days you can start smoking/using the product from 06:30AM

The following activities will take place during Date 31 and Date 61:

- Support for smoking abstinence if needed (Arm 3 only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry), and risk marker analysis after at least 10 hours fasting period.
- End of 24-hour urine collection from Day 30 or Day 60. From the collected urine over the 24 hour, biomarkers of exposure, creatinine and risk markers will be analyzed.
- Assessment of Cough (a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)



- A urine safety analysis
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product

Day 90 Visit. (from check in prior 08:30 AM on Day 90, until discharge on Day 91)

You will be asked to bring enough THS Menthol Tobacco Sticks you have been using to cover your stay at the clinic. THS Menthol Tobacco Sticks will be resupplied during your stay at the clinic.

If you are assigned to THS 2.2 arm, for this visit you will have to bring all empty or unused packs and unused THS 2.2 tobacco sticks. You will also have to bring the Tobacco Heating Device (including all parts - holders, the charger, a cleaning tool, a mains power supply, and a USB cable) and e-diary. You will leave all these supplies at the site at Day 91, at the discharge.

Smoking or product use will be allowed on site from your check in prior to around 11:00PM and on Day 91 only after, CYP2A6 activity measurement and spirometry have been performed. There is no restriction for smoking / product use prior to check in on site. If you have been allocated to the menthol conventional cigarette arm or the smoking abstinence arm, you will not be allowed use the THS 2.2 Menthol product.

During Day 90 Visit, you will be asked to continue completing your e-diary on a daily basis.

Day 90

The following activities will take place during Day 90:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- Human smoking topography (to assess your smoking behavior) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device must be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms over a period of 4 hours each day and only with the product you are assigned to.
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device).
- 24-hour urine collection will take place from the morning of Day 90, until the morning of Day 91 (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information



concerning the method of urine collection

- You will take a tablet of caffeine approximately 200 mg with approximately 240 ml of water
- You will have a carbon monoxide breath test
- Collection of a blood sample to measure carboxyhemoglobin
- Collection of a blood sample to measure nicotine and cotinine in your blood
- Collection of a blood sample to measure CYP1A2 activity – this will take place 6 hours after you have taken the caffeine tablet
- Nasal Epithelial collection (“collections of the cells from the nose”) and buccal sample collection (“collection of the cells from the mouth”), only if you have signed the optional informed consent for these procedures. These procedures will be explained to you in more detail if you sign the informed consent form for these procedures.
- Questionnaire of Smoking Urges (desire to smoke) - You will be asked to complete a questionnaire to indicate your craving.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate the product
- You will be asked if you are seriously thinking of quitting smoking in the next 6 months or less (by answering the Prochaska “Stage of Change” questionnaire).
- You will be asked to fill out a specific questionnaire about your nicotine dependence (Fagerstrom Test for Nicotine Dependence).

Please note that all used Menthol Tobacco Sticks will be collected. In the THS 2.2 arm, subjects will be asked to collect every used tobacco plug into dedicated vials which will be provided by the staff

Day 91

You may be woken up very early in the morning in order to allow enough time to complete all of the study procedures required.

During this day the following procedures will take place:

- Support for smoking abstinence if needed (smoking abstinence arm only)
- You will be asked how you are feeling and about any medications that you are currently taking.
- A blood sample to measure CYP2A6 activity in your blood. This blood sample will be taken before you smoke or use the THS 2.2 Menthol product.
- A blood sample will be collected to measure carboxyhemoglobin – (prior to full lung function test).
- Full lung function tests will be done (spirometry with bronchodilator, and two other techniques using the spirometer). All the assessments have to be done prior to product use.

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- Collection of blood samples in order to perform laboratory tests (hematology, clinical chemistry) and risk markers – after at least 10 hours fasting period.
- A blood sample to measure oxysterols - after at least 10 hours fasting period
- A urine safety test, and a urine pregnancy test for all women
- Physical examination including weight, waist circumference and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- You will have an electrocardiogram - a painless heart rhythm tracing.
- Collection of blood samples for long term storage of serum and plasma for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period - , only if you have signed the optional informed consent for these procedures.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis after at least 10 hours fasting period -, only if you have signed the optional informed consent for these procedures
- End of 24-hour urine collection that started on Day 90. From the collected urine over the 24 hours, biomarkers of exposure, creatinine and risk markers will be analyzed, a mutagenicity test will be done. Urine samples will be kept for long term bio-storage and further analysis if consent was given for this procedure.
- Start of 4 hour urine collection on Day 91 (from 10:00AM and for a period of 4 hours, each time you will urinate into disposable containers which will then be handed over to the site staff. From the collected urine, biomarkers of exposure and risk makers will be analyzed.
- You will be given advice on the risk of smoking/smoking cessation advice and debriefing on the THS 2.2 Menthol product
- You will be asked to complete an assessment of Cough (a questionnaire assessing your cough) and the Minnesota Nicotine Withdrawal Scale (a questionnaire to evaluate signs and symptoms of withdrawal)
- Before leaving the site you will hand over to the site staff THS 2.2 Menthol Device, unused THS2.2 Tobacco Sticks (if you are in arm 1) and E-diary

Safety Follow-up Period

A safety follow-up period will occur for 28 days after the last planned study visit (discharge on Day 91 or early termination). If you withdraw from the study earlier you will enter into the follow-up period on the day of your withdrawal.

If you participated on the product trial on Day -2 but you were not enrolled in the study, you will still enter the 28-days safety follow up.

During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problem that you report during the study or during the follow-up period and that has not been resolved following discharge from the site.

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**Withdrawal Procedures**

If you withdraw early from the study, for any reason, you may be asked to complete the lab testing and procedures outlined in the Day 6 section listed above.

You will not be allowed to bring your own food or drink into the investigational site. Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor. Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period. Consumption of water is also allowed without any restriction. A standard menu and meal schedule will be provided for all participants in all study arms.

Blood and Urine Samples

Approximately 316 mL of blood, (about 1 and ¼ cups), will be drawn throughout the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about 2 cups) of blood.

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn includes 40 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further analysis of biomarkers exposure in the body and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given).

Additional blood samples may be required if any of your lab values are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health. The blood samples collected will be analyzed using validated methods except for oxysterol that will be analyzed by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

Blood and urine samples for safety laboratory testing will be measured on site or at a designated laboratory and will be kept for approximately 2 months, after which they will be destroyed.

All blood and urine sampling for the measurement of biomarkers of exposure and risk markers will be analyzed and kept according to relevant laboratory documentation.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.



All data collected will be stored for as long as necessary under applicable law, regulations and standards, to ensure that the data are available for inspections of the study by regulatory bodies and ensure the integrity of the study.

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this use, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens

Research Participant Responsibilities

As a research participant you will be asked to complete the study procedures for this study, come to the study clinic for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

General Restrictions

- To avoid cross contamination from different products, Arm 1 (THS 2.2 Menthol) and Arm 2 (menthol conventional cigarettes) must use their assigned products in separate smoking booths. Arm 3 (smoking abstinence) will not be allowed in the smoking area.
- You must not have used prescription medications OR over-the-counter medications for 4 weeks prior to the start, of the study and throughout the study, including the safety follow up period. Please tell the study doctor about any medicines (including prescription, over-the-counter drugs, and vitamins/herbal supplements) that you are taking. He will be able to tell you if you are allowed to take it during the study or not.
- You must not have participated in an investigational research study within the last 3 months.
- You must not have donated either blood or plasma (eg, plasmapheresis) within 3 months prior to admission.

If you are assigned to Arm 1 you will not be allowed to smoke any menthol conventional cigarettes, or use any nicotine/tobacco-containing products (including Nicotine Replacement Therapy) from Day 1 (06:30 AM) until the time of Discharge on Day 6.

Dietary Restrictions

- Standardized (and calorie controlled) meals and snacks will be served at regular times during your clinic confinement except when fasting is required or otherwise noted
- During the confinement period, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted.



- No alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be allowed during the confinement period.
- Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the confinement period.
- 1 day prior to the Day 90 Visit, you must refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the outpatient visit.
- You will not be allowed to bring your own food or drink into the investigational site.
- Meals will be served according to pre-determined schedules for this study. If you have any questions regarding meals, please speak with your study doctor.
- Additional light snacks, fruits, and raw vegetables will be available to you without restrictions at any time during the confinement period.
- Consumption of water is also allowed without any restriction.
- A standard menu and meal schedule will be provided for all participants in all study arms.

RISKS AND DISCOMFORTS

There may be risks to you if you participate in this study. As a tobacco consumer, the risks associated with the use of your normal type of tobacco product will remain the same. At this time, the use of the THS 2.2 Menthol product does not provide any less risk of tobacco related diseases than your usual brand cigarette product(s).

Smoking is addictive and causes serious, fatal diseases such as lung cancer, pulmonary and cardiovascular diseases (heart disease), and other serious diseases in smokers. There are no safe cigarettes. Only smoking cessation has been shown to reduce the risk of smoking-related diseases in smokers. Despite the risks which are attributable to smoking, some smokers have difficulty in giving up smoking or decide to continue smoking.

Smoking tobacco is harmful, and medical studies have proven that smoking tobacco is among the leading causes of many diseases. With your consent, you will be provided with further information on the risks related to smoking and smoking cessation advice during your visits.

You may also experience withdrawal symptoms and cravings throughout the study, depending on your Arm assignment. It is possible that during this period you may experience some nicotine withdrawal symptoms which are known to include: cravings for tobacco, irritation, anger, concentration problems, headaches, fatigue, constipation, restlessness, insomnia, dizziness, and anxiety.

The particular use of the THS 2.2 Menthol product may involve risks to the subject (or to

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the embryo or fetus, if the subject is or may become pregnant). These risks are currently unforeseeable.

If you have private medical insurance you may need to let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance.

There is a possibility that the various tests performed during the study could find a medical condition which you did not previously know about. If this happens, your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your Primary Care doctor.

You will not be permitted to use nicotine replacement therapy or other products supportive of smoking cessation during your stay at the clinic.

Please note that all doctors employed by the investigational site are trained and certified in advanced life support procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

In previous clinical studies, earlier versions of THS 2.2 Menthol have been tested, and showed no safety concerns. However, by participating to this study, you may experience some events (including but not limited to headache, pain to blood draw, dizziness). You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

There may be other risks to you while being in this study. You may experience some discomfort associated with the use of THS 2.2 Menthol that has not previously been reported. There may be some unknown or infrequent and unforeseeable risks associated with the use of this study product, including allergic reaction or interaction with drugs and medications that you are taking. Other serious unknown side effects may also be possible, including death.

All of these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the course of the study, a team of trained Investigators and nurses will monitor your health and safety.

If you experience any of the above side effects or other symptoms, you should notify the Study Doctor or study staff immediately. If you do not provide this information to the Study doctor and study staff regarding any side effects, you may unintentionally allow yourself to be harmed by participating in this study.

Ask the Study Doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

To reduce the chance of injury, always use the Device in accordance with the manufacturer's instructions. Warnings and safety instructions included in the User Manual cannot cover all possible conditions and situations that could occur. Refer to

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the User Manual for more information.

STUDY PROCEDURE RISKS

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

X-rays - If you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure.

Spirometry – for this procedure a short-acting bronchodilator (drug that will ‘open up’ the lungs) will be used. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these products, including severe or life threatening allergic reactions or unexpected interactions with another medication. You will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

If you experience an injury, bad effect, or any other unusual health experience during this study, you should immediately contact the study doctor or the study staff.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of smoking on the unborn child are known to be hazardous. In order to take part in this study, you must not be pregnant. It is important that you use the following appropriate forms of birth control during the duration of the study and until the end of the safety follow-up period, and that females do not become pregnant, or breastfeed a baby.

- Intrauterine device or intrauterine system (IUD),
- established use of oral/injectable/implantable /transdermal hormonal methods,
- barrier methods of contraception



- condoms or occlusive caps (diaphragm) with spermicidal foam/gel/film/suppository,
- vasectomized partner(s), or
- true abstinence (periodic abstinence and withdrawal are not effective methods)

Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menstrual cycles for greater than 12 months. A follicle stimulating hormone test must be performed and must be within acceptable limits.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the IRB.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have. You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

This study is for research purposes only. There is no direct benefit to you from your participation in the study except that you will receive a health check-up and smoking cessation advice. Results from the study will help the Sponsor gain a better understanding of the safety of THS 2.2 Menthol and how well the body absorbs its nicotine. This information may help people in the future.

TREATMENT ALTERNATIVES

No study drug is being given in this study. Therefore, alternative treatment is not applicable as part of this study. However, if you decide that you wish to give up smoking, study personnel will provide you information on how to seek support to give up smoking.

COST

There is no cost for participating in this research study. The THS 2.2 Menthol product, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

COMPENSATION FOR BEING IN THIS STUDY

You will be compensated for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. You will be compensated according to the schedule below.

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Compensation Schedule

Screening Visit	-0-
Screening chest x X-ray visit	\$50.00
Research unit Confinement Nights (11 nights x \$250.00)	\$2750.00
Extended Out Patient Visit (3 visits x \$200)	\$600.00
Diaries (per week) 14 weeks x \$100	\$1400.00
Study Completion	\$720.00
TOTAL	\$5520.00

Total compensation for study completion will be \$5520. If you choose to withdraw from the research study, you will receive compensation only for the portion of the study that you have completed as outlined above. If menthol conventional cigarettes had to be purchased for you by Covance because you ran out during the confinement period, the amount spent will be deducted from your total compensation.

If you are withdrawn from the study early due to a significant medical event or cancellation by the sponsor, you will be compensated an amount for the portion of the study completion compensation based on the number of visits you completed.

If you are selected as an alternate and not selected to participate in the study you will be compensated \$250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be compensated.

All research participants will receive their compensation within 21 days of the completion of their participation in the study.

If you take part in this study, you agree that you will not be considered to be an employee of Covance or Philip Morris Products S.A.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to Covance, if you have one. If you receive more than \$600 in one calendar year from Covance, you will receive a 1099 tax form the following January. Covance reports the money you receive to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Covance to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a tax professional to assist you.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

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Your participation in this study is voluntary. You are free to withdraw from this study at any time; however, you should inform the study doctor immediately if you intend to withdraw. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time. You may take away your consent to use and disclose your information at any time. If you withdraw your consent, you will not be able to stay in this study. If you do withdraw, or leave the study early, for any reason, you will be asked to complete the procedures in Discharge Day 6.

The study sponsor or doctor in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow the instructions of the Study Team
- If the study is stopped by the sponsor and/or doctors participating in the study prior to completion or the sponsor asks that you be removed from the study.

CONFIDENTIALITY

If you agree to take part in the research study, information about your identity, health and your participation will be collected, recorded, and stored by the study staff.

The Sponsor and its representatives, the US Food and Drug Administration (FDA), other health authorities and MidLands Independent Review Board may inspect your hard-copy and electronically stored research medical records which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

Because of the need to use information as noted above, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s),

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and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants).

WHO HAS REVIEWED THE STUDY?

MidLands Independent Review Board (MLIRB) has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for the Covance Daytona Beach Clinical Research Unit is 386-366-6400.

Covance will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer. You are not barred from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research

You **DO NOT** waive any of your legal rights by signing this form.

EMERGENCY CONTACT

During the study, if you experience any medical problems, or suffer a research-related injury, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like



information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CLOSING STATEMENT

You have carefully read the above information. You have also received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

PRIMARY CARE DOCTOR NOTIFICATION

After all your eligibility tests are received and it has been determined that you are eligible to enter the study, we will notify your private doctor that you are participating in this research study if you want us to. Please check your preference below:

- ☐ Yes, I want the study doctor to inform my private doctor of my participation in this study.

Name and address and phone number of private doctor

- ☐ No, I do not want the study doctor to inform my private doctor of my participation in this study.
- ☐ I do not have a private doctor

**SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

- I have read the above information in a language that I understand well.
- The content and meaning of this information has been explained to me.
- I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
- I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.
- I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
- I also agree to the HIV testing as described in this document.
- I voluntarily and freely donate any and all blood and urine samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.
- I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time**I have received a signed and dated copy of this study consent form to keep.**_____
Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

Date: 14 Apr 2014

Version No. 6

Page 30 of 32

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US

**AUTHORIZATION AND CONSENT TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH**

During your participation in this research study, the study doctor and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called "Protected Health Information" (or "PHI").

Where applicable under federal law (the "Privacy Rule") or other applicable laws, your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission or consent. This permission and consent is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor and study staff to disclose PHI to the persons and groups described below:

- To the sponsor of this study (SPONSOR) and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records, which means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records or receive information relating to specimens that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.
- The Independent Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.



Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with applicable law, your PHI may no longer be protected by law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records. This Authorization has no expiration date from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor at the address listed on the first page of this form, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this signed and dated Authorization after you have signed it.

Signature of Subject

Date

Printed Name of Subject

Signature of the Person Obtaining the
Authorization

Date

Printed Name of the Person Obtaining the
Authorization

To be Completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY
APR 14 2014
MLIRB
Medical Independent Review Board



**16.1.3.18.2 INFORMED CONSENT DOCUMENT FOR GENETIC AND
PHARMACOGENOMIC ANALYSIS**

**INFORMED CONSENT DOCUMENT FOR GENETIC AND PHARMACOGENOMIC ANALYSIS**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This sub-study consent form informs you about optional assessments which will be conducted in subjects that agreed to participate in the main study. This subject information and informed consent form is an addition to the main study consent form that you have already signed. The



intention of this document is to give you information so that you can decide if you want to participate to this optional sub-study.

You are being asked to allow the collection of a sample of your blood as well as nasal and buccal (from the mouth) samples. Genetic analysis will then be conducted on these samples. Having your samples drawn for this genetic research is voluntary. You do not have to agree to be in the genetic research study to take part in the main study.

Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this research sub-study. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given a copy of it to keep. If you do not agree to participate in the genetic research study, this does not prevent you from participating to the main study.

You must have reviewed and signed the main study informed consent before you review this consent form.

This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

By signing this consent form you agree to the collection and storage of blood, nasal and buccal samples for further pharmacogenomic analysis. Pharmacogenomics assesses how your specific genetic makeup handles a drug.

This form may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this sub-study. Before you decide to take part, you must understand the purpose of this optional sub-study, any potential risks to you, and what is expected of you during this sub-study. Even if you agree to participate in this optional sub-study you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this optional sub-study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**NATURE AND PURPOSE**

When people are exposed to a substance or a mix of substances (e.g., food, smoke, drug), reactions in the body may be triggered. These reactions or responses will vary between each person, since each person has a different genetic material (genes).

Once the substance is absorbed by the body, it might affect the level of expression of these genes. These genes might then influence the time that some of the substances might remain in the body, how they are broken down or why some people might react differently to them.

Cells are the building blocks of the human body and each type of cell is specially adapted to its specific function in the body. All cells contain proteins that are produced from a substance called messenger ribonucleic acid (mRNA) and allow the cells to function.

The purpose of this sub-study is to collect the blood, nasal and buccal samples for analysis and investigations on how the smokers will respond to the aerosol (smoke) generated by the product THS 2.2, as compared to the subjects who are exposed to the smoke from conventional cigarettes, or as compared to a group of subjects who abstain from smoking ce).

The evaluation of these differences may provide insight into the biological processes that take place when using the study product as compared to conventional cigarettes or smoking abstinence. It will also allow us to compare if there are differences in the level of expression of these genes within a smoker between the mouth and the nose.

The samples will also be collected for determination of the quantity and quality of the RNA (pharmacogenomic) in blood samples to understand if the deleterious effect of smoking conventional cigarettes on cellular function could be decreased when switching to the test product or by smoking abstinence.

STUDY PROCEDURES

If you agree to participate in this sub-study, you will have the following three additional sample collection procedures:

Nasal epithelial collection ("collections of the cells from the nose") procedure (Day 0, Day 6 and Day 90)

You will be asked to blow your nose. This procedure will be performed on the left nostril only. If you wish to have the nostril numbed for the procedure, an anesthetic spray containing 1% Lidocaine will be used. A nasal speculum (device that resembles pliers) will be inserted to widen the left nostril, and then a soft brush will be inserted into the nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed. A second soft brush will be inserted into the same nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed.

Buccal sample collection ("collection of the cells from the mouth") procedure (Day 0, Day 6 and Day 90)

You will be asked to rinse out your mouth with water (about 4 teaspoons, 20 ml) that will be provided to you. A sterile brush will be inserted in your mouth and pushed slightly against the side of your mouth (inner cheek) until the shaft bends. The brush will be then rotated for about 10 seconds and the operation repeated with the other cheek.

**Blood collection for transcriptomics (Day 0 and Day 90)**

Two additional blood samples for this type of analysis will be drawn (about 2 teaspoons, 10 ml in total). Specifically, one blood sample will be required from you at the beginning of the study (Day 0), and another one at the end of the study (Day 90).

STUDY PROCEDURE RISKS

During the collection of nasal and mouth samples, side effects that may occur include burning, pain, stinging, and nasal irritation. In rare cases, a nose bleed may occur. If you choose to have your nostrils to be numbed, the lidocaine spray may cause some allergic reactions and numbness. If misused, the lidocaine could cause serious side effects such as difficulty in breathing, swelling in the mouth or face and pain in the chest.

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

OTHER POTENTIAL RISKS

There are possible non-physical risks associated with this genetic research, such as the risks associated with a breach of privacy or confidentiality. Breach of confidentiality, may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to you or your family. Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

CONFIDENTIALITY

All of your samples will be given a code. This code will contain your age, sex, race, and other information. It will not contain your name or initials. As long as the samples are stored at the main study site they can be linked to you. Before samples are sent out from the main study site to an outside laboratory for analysis, they will be anonymized. This means that the link between you and the sample code will be deleted and there will be no possibility to trace the samples back to you. Anonymization is intended to prevent your re-identification.

The samples will be sent to the outside laboratory for analysis after all other data collected during the main study have been entered into a database (approximately 3-4 months after the last volunteer completed the study). As anonymized samples and associated data are not traceable back to you, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at your request if this is done after the samples are sent from the study site for analysis.

WITHDRAWAL OF SAMPLES

As explained above, it is your choice if you want to be in this sub-study. You can stop donating your biological samples at any time. Your decision to discontinue the participation to this sub-study does not impact your participation to the main study.

Your main study doctor will keep records that link your personal information with your coded samples until the shipment of the samples to an outside laboratory for analysis. Before the



samples leave the study site the link will be deleted. If you withdraw your consent for the sub-study prior to deletion of this link, you may request your samples to be destroyed by the researchers and no longer used in research. If you withdraw your consent after the samples leave the study site, there will be no possibility to track them back to you and therefore it will be not possible to destroy them, or to exclude those samples from further analysis.

Sponsor and researchers working on its behalf shall be entitled to keep and use any research results that they obtain from your samples which were taken prior to your withdrawal of the consent.

BENEFITS

There is no direct benefit to you by taking part in this study. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor your study doctor will be contacted by the researchers in connection with the research or any information about the results of the tests performed on the samples from this sub-study.

ALTERNATIVE

You have the choice not to take part in this optional sub-study.

COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$150.00

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

WHO HAS REVIEWED THE STUDY?

MLIRB Independent Review Board has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 214-920-9053.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

**PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS**

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

**CONSENT AND SIGNATURES**

Please read the following paragraph out loud to the person obtaining the consent.

I have read the above information in a language, which I understand well. The content and meaning of this information has been explained to me.

I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy

Signature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

APPROVED BY
JUL 02 2013
MLIRB
Montréal Independent Review Board

**INFORMED CONSENT DOCUMENT FOR GENETIC AND PHARMACOGENOMIC ANALYSIS**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1900 Mason Avenue, Suite 140 Daytona Beach, FL, 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This sub-study consent form informs you about optional assessments which will be conducted in subjects that agreed to participate in the main study. This subject information and informed consent form is an addition to the main study consent form that you have already signed. The



intention of this document is to give you information so that you can decide if you want to participate to this optional sub-study.

You are being asked to allow the collection of a sample of your blood as well as nasal and buccal (from the mouth) samples. Genetic analysis will then be conducted on these samples. Having your samples drawn for this genetic research is voluntary. You do not have to agree to be in the genetic research study to take part in the main study.

Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this research sub-study. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given a copy of it to keep. If you do not agree to participate in the genetic research study, this does not prevent you from participating to the main study.

You must have reviewed and signed the main study informed consent before you review this consent form.

This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

By signing this consent form you agree to the collection and storage of blood, nasal and buccal samples for further pharmacogenomic analysis. Pharmacogenomics assesses how your specific genetic makeup handles a drug.

This form may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this sub-study. Before you decide to take part, you must understand the purpose of this optional sub-study, any potential risks to you, and what is expected of you during this sub-study. Even if you agree to participate in this optional sub-study you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this optional sub-study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**NATURE AND PURPOSE**

When people are exposed to a substance or a mix of substances (e.g., food, smoke, drug), reactions in the body may be triggered. These reactions or responses will vary between each person, since each person has a different genetic material (genes).

Once the substance is absorbed by the body, it might affect the level of expression of these genes. These genes might then influence the time that some of the substances might remain in the body, how they are broken down or why some people might react differently to them.

Cells are the building blocks of the human body and each type of cell is specially adapted to its specific function in the body. All cells contain proteins that are produced from a substance called messenger ribonucleic acid (mRNA) and allow the cells to function.

The purpose of this sub-study is to collect the blood, nasal and buccal samples for analysis and investigations on how the smokers will respond to the aerosol (smoke) generated by the product THS 2.2, as compared to the subjects who are exposed to the smoke from conventional cigarettes, or as compared to a group of subjects who abstain from smoking ce).

The evaluation of these differences may provide insight into the biological processes that take place when using the study product as compared to conventional cigarettes or smoking abstinence. It will also allow us to compare if there are differences in the level of expression of these genes within a smoker between the mouth and the nose.

The samples will also be collected for determination of the quantity and quality of the RNA (pharmacogenomic) in blood samples to understand if the deleterious effect of smoking conventional cigarettes on cellular function could be decreased when switching to the test product or by smoking abstinence.

STUDY PROCEDURES

If you agree to participate in this sub-study, you will have the following three additional sample collection procedures:

Nasal epithelial collection ("collections of the cells from the nose") procedure (Day 0, Day 6 and Day 90)

You will be asked to blow your nose. This procedure will be performed on the left nostril only. If you wish to have the nostril numbed for the procedure, an anesthetic spray containing 1% Lidocaine will be used. A nasal speculum (device that resembles pliers) will be inserted to widen the left nostril, and then a soft brush will be inserted into the nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed. A second soft brush will be inserted into the same nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed.

Buccal sample collection ("collection of the cells from the mouth") procedure (Day 0, Day 6 and Day 90)

You will be asked to rinse out your mouth with water (about 4 teaspoons, 20 ml) that will be provided to you. A sterile brush will be inserted in your mouth and pushed slightly against the side of your mouth (inner cheek) until the shaft bends. The brush will be then rotated for about 10 seconds and the operation repeated with the other cheek.

**Blood collection for transcriptomics (Day 0 and Day 90)**

Two additional blood samples for this type of analysis will be drawn (about 2 teaspoons, 10 ml in total). Specifically, one blood sample will be required from you at the beginning of the study (Day 0), and another one at the end of the study (Day 90).

STUDY PROCEDURE RISKS

During the collection of nasal and mouth samples, side effects that may occur include burning, pain, stinging, and nasal irritation. In rare cases, a nose bleed may occur. If you choose to have your nostrils to be numbed, the lidocaine spray may cause some allergic reactions and numbness. If misused, the lidocaine could cause serious side effects such as difficulty in breathing, swelling in the mouth or face and pain in the chest.

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

OTHER POTENTIAL RISKS

There are possible non-physical risks associated with this genetic research, such as the risks associated with a breach of privacy or confidentiality. Breach of confidentiality, may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to you or your family. Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

CONFIDENTIALITY

All of your samples will be given a code. This code will contain your age, sex, race, and other information. It will not contain your name or initials. As long as the samples are stored at the main study site they can be linked to you. Before samples are sent out from the main study site to an outside laboratory for analysis, they will be anonymized. This means that the link between you and the sample code will be deleted and there will be no possibility to trace the samples back to you. Anonymization is intended to prevent your re-identification.

The samples will be sent to the outside laboratory for analysis after all other data collected during the main study have been entered into a database (approximately 3-4 months after the last volunteer completed the study). As anonymized samples and associated data are not traceable back to you, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at your request if this is done after the samples are sent from the study site for analysis.

WITHDRAWAL OF SAMPLES

As explained above, it is your choice if you want to be in this sub-study. You can stop donating your biological samples at any time. Your decision to discontinue the participation to this sub-study does not impact your participation to the main study.

Your main study doctor will keep records that link your personal information with your coded samples until the shipment of the samples to an outside laboratory for analysis. Before the



samples leave the study site the link will be deleted. If you withdraw your consent for the sub-study prior to deletion of this link, you may request your samples to be destroyed by the researchers and no longer used in research. If you withdraw your consent after the samples leave the study site, there will be no possibility to track them back to you and therefore it will be not possible to destroy them, or to exclude those samples from further analysis.

Sponsor and researchers working on its behalf shall be entitled to keep and use any research results that they obtain from your samples which were taken prior to your withdrawal of the consent.

BENEFITS

There is no direct benefit to you by taking part in this study. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor your study doctor will be contacted by the researchers in connection with the research or any information about the results of the tests performed on the samples from this sub-study.

ALTERNATIVE

You have the choice not to take part in this optional sub-study.

COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$150.00

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

WHO HAS REVIEWED THE STUDY?

MLIRB Independent Review Board has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 386-366-6400.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

**PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS**

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI at 386-366-6400.

LEGAL RIGHTS

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**CONSENT AND SIGNATURES**

Please read the following paragraph out loud to the person obtaining the consent.

I have read the above information in a language, which I understand well. The content and meaning of this information has been explained to me.

I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy

Signature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY

JUL 02 2013

MLIRB
Mutual Independent Review Board

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

**INFORMED CONSENT DOCUMENT FOR GENETIC AND PHARMACOGENOMIC ANALYSIS**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This sub-study consent form informs you about optional assessments which will be conducted in subjects that agreed to participate in the main study. This subject information and informed consent form is an addition to the main study consent form that you have already signed. The



intention of this document is to give you information so that you can decide if you want to participate to this optional sub-study.

You are being asked to allow the collection of a sample of your blood as well as nasal and buccal (from the mouth) samples. Genetic analysis will then be conducted on these samples. Having your samples drawn for this genetic research is voluntary. You do not have to agree to be in the genetic research study to take part in the main study.

Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this research sub-study. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given a copy of it to keep. If you do not agree to participate in the genetic research study, this does not prevent you from participating to the main study.

You must have reviewed and signed the main study informed consent before you review this consent form.

This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

By signing this consent form you agree to the collection and storage of blood, nasal and buccal samples for further pharmacogenomic analysis. Pharmacogenomics assesses how your specific genetic makeup handles a drug.

This form may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this sub-study. Before you decide to take part, you must understand the purpose of this optional sub-study, any potential risks to you, and what is expected of you during this sub-study. Even if you agree to participate in this optional sub-study you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this optional sub-study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**NATURE AND PURPOSE**

When people are exposed to a substance or a mix of substances (e.g., food, smoke, drug), reactions in the body may be triggered. These reactions or responses will vary between each person, since each person has a different genetic material (genes).

Once the substance is absorbed by the body, it might affect the level of expression of these genes. These genes might then influence the time that some of the substances might remain in the body, how they are broken down or why some people might react differently to them.

Cells are the building blocks of the human body and each type of cell is specially adapted to its specific function in the body. All cells contain proteins that are produced from a substance called messenger ribonucleic acid (mRNA) and allow the cells to function.

The purpose of this sub-study is to collect the blood, nasal and buccal samples for analysis and investigations on how the smokers will respond to the aerosol (smoke) generated by the product THS 2.2, as compared to the subjects who are exposed to the smoke from conventional cigarettes, or as compared to a group of subjects who abstain from smoking ce).

The evaluation of these differences may provide insight into the biological processes that take place when using the study product as compared to conventional cigarettes or smoking abstinence. It will also allow us to compare if there are differences in the level of expression of these genes within a smoker between the mouth and the nose.

The samples will also be collected for determination of the quantity and quality of the RNA (pharmacogenomic) in blood samples to understand if the deleterious effect of smoking conventional cigarettes on cellular function could be decreased when switching to the test product or by smoking abstinence.

STUDY PROCEDURES

If you agree to participate in this sub-study, you will have the following three additional sample collection procedures:

Nasal epithelial collection ("collections of the cells from the nose") procedure (Day 0, Day 6 and Day 90)

You will be asked to blow your nose. This procedure will be performed on the left nostril only. If you wish to have the nostril numbed for the procedure, an anesthetic spray containing 1% Lidocaine will be used. A nasal speculum (device that resembles pliers) will be inserted to widen the left nostril, and then a soft brush will be inserted into the nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed. A second soft brush will be inserted into the same nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed.

Buccal sample collection ("collection of the cells from the mouth") procedure (Day 0, Day 6 and Day 90)

You will be asked to rinse out your mouth with water (about 4 teaspoons, 20 ml) that will be provided to you. A sterile brush will be inserted in your mouth and pushed slightly against the side of your mouth (inner cheek) until the shaft bends. The brush will be then rotated for about 10 seconds and the operation repeated with the other cheek.

**Blood collection for transcriptomics (Day 0 and Day 90)**

Three additional blood samples for this type of analysis will be drawn (about 3 teaspoons, 15 ml in total). Specifically, one blood sample will be required from you at the beginning of the study on Day 0, a second blood sample on Day 6, and a third sample at the end of the study on Day 91.

STUDY PROCEDURE RISKS

During the collection of nasal and mouth samples, side effects that may occur include burning, pain, stinging, and nasal irritation. In rare cases, a nose bleed may occur. If you choose to have your nostrils to be numbed, the lidocaine spray may cause some allergic reactions and numbness. If misused, the lidocaine could cause serious side effects such as difficulty in breathing, swelling in the mouth or face and pain in the chest.

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

OTHER POTENTIAL RISKS

There are possible non-physical risks associated with this genetic research, such as the risks associated with a breach of privacy or confidentiality. Breach of confidentiality, may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to you or your family. Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

CONFIDENTIALITY

All of your samples will be given a code. This code will contain your age, sex, race, and other information. It will not contain your name or initials. As long as the samples are stored at the main study site they can be linked to you. Before samples are sent out from the main study site to an outside laboratory for analysis, they will be anonymized. This means that the link between you and the sample code will be deleted and there will be no possibility to trace the samples back to you. Anonymization is intended to prevent your re-identification.

The samples will be sent to the outside laboratory for analysis after all other data collected during the main study have been entered into a database (approximately 3-4 months after the last volunteer completed the study). As anonymized samples and associated data are not traceable back to you, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at your request if this is done after the samples are sent from the study site for analysis.

WITHDRAWAL OF SAMPLES

As explained above, it is your choice if you want to be in this sub-study. You can stop donating your biological samples at any time. Your decision to discontinue the participation to this sub-study does not impact your participation to the main study.



Your main study doctor will keep records that link your personal information with your coded samples until the shipment of the samples to an outside laboratory for analysis. Before the samples leave the study site the link will be deleted. If you withdraw your consent for the sub-study prior to deletion of this link, you may request your samples to be destroyed by the researchers and no longer used in research. If you withdraw your consent after the samples leave the study site, there will be no possibility to track them back to you and therefore it will be not possible to destroy them, or to exclude those samples from further analysis.

Sponsor and researchers working on its behalf shall be entitled to keep and use any research results that they obtain from your samples which were taken prior to your withdrawal of the consent.

BENEFITS

There is no direct benefit to you by taking part in this study. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor your study doctor will be contacted by the researchers in connection with the research or any information about the results of the tests performed on the samples from this sub-study.

ALTERNATIVE

You have the choice not to take part in this optional sub-study.

COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$150.00

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

WHO HAS REVIEWED THE STUDY?

MLIRB Independent Review Board has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 214-920-9053.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

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I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY
APR 14 2014
MLIRB
Medtronic Independent Review Board

Version#: 2

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US

**INFORMED CONSENT DOCUMENT FOR GENETIC AND PHARMACOGENOMIC ANALYSIS**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1900 Mason Avenue, Suite 140 Daytona Beach, FL, 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

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intention of this document is to give you information so that you can decide if you want to participate to this optional sub-study.

You are being asked to allow the collection of a sample of your blood as well as nasal and buccal (from the mouth) samples. Genetic analysis will then be conducted on these samples. Having your samples drawn for this genetic research is voluntary. You do not have to agree to be in the genetic research study to take part in the main study.

Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this research sub-study. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given a copy of it to keep. If you do not agree to participate in the genetic research study, this does not prevent you from participating to the main study.

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BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**NATURE AND PURPOSE**

When people are exposed to a substance or a mix of substances (e.g., food, smoke, drug), reactions in the body may be triggered. These reactions or responses will vary between each person, since each person has a different genetic material (genes).

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STUDY PROCEDURES

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You will be asked to rinse out your mouth with water (about 4 teaspoons, 20 ml) that will be provided to you. A sterile brush will be inserted in your mouth and pushed slightly against the side of your mouth (inner cheek) until the shaft bends. The brush will be then rotated for about 10 seconds and the operation repeated with the other cheek.

**Blood collection for transcriptomics (Day 0 and Day 90)**

Three additional blood samples for this type of analysis will be drawn (about 3 teaspoons, 15 ml in total). Specifically, one blood sample will be required from you at the beginning of the study on Day 0, a second blood sample on Day 6 and a third sample at the end of the study on Day 91.

STUDY PROCEDURE RISKS

During the collection of nasal and mouth samples, side effects that may occur include burning, pain, stinging, and nasal irritation. In rare cases, a nose bleed may occur. If you choose to have your nostrils to be numbed, the lidocaine spray may cause some allergic reactions and numbness. If misused, the lidocaine could cause serious side effects such as difficulty in breathing, swelling in the mouth or face and pain in the chest.

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

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There are possible non-physical risks associated with this genetic research, such as the risks associated with a breach of privacy or confidentiality. Breach of confidentiality, may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to you or your family. Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

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WITHDRAWAL OF SAMPLES

As explained above, it is your choice if you want to be in this sub-study. You can stop donating your biological samples at any time. Your decision to discontinue the participation to this sub-study does not impact your participation to the main study.



Your main study doctor will keep records that link your personal information with your coded samples until the shipment of the samples to an outside laboratory for analysis. Before the samples leave the study site the link will be deleted. If you withdraw your consent for the sub-study prior to deletion of this link, you may request your samples to be destroyed by the researchers and no longer used in research. If you withdraw your consent after the samples leave the study site, there will be no possibility to track them back to you and therefore it will be not possible to destroy them, or to exclude those samples from further analysis.

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You have the choice not to take part in this optional sub-study.

COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$150.00

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WHO HAS REVIEWED THE STUDY?

MLIRB Independent Review Board has reviewed the objectives and the proposed conduct of the main study.

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I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.
I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
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I have received a copy of this signed and dated study consent form to keep.

Your Signature

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Version#: 2
Approved by MLIRB on 04/14/14
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APPROVED BY
APR 14 2014
MLIRB
Michigan Independent Review Board

**INFORMED CONSENT DOCUMENT FOR GENETIC AND PHARMACOGENOMIC ANALYSIS**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This sub-study consent form informs you about optional assessments which will be conducted in subjects that agreed to participate in the main study. This subject information and informed consent form is an addition to the main study consent form that you have already signed. The



intention of this document is to give you information so that you can decide if you want to participate to this optional sub-study.

You are being asked to allow the collection of a sample of your blood as well as nasal and buccal (from the mouth) samples. Genetic analysis will then be conducted on these samples. Having your samples drawn for this genetic research is voluntary. You do not have to agree to be in the genetic research study to take part in the main study.

Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this research sub-study. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given a copy of it to keep. If you do not agree to participate in the genetic research study, this does not prevent you from participating to the main study.

You must have reviewed and signed the main study informed consent before you review this consent form.

This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

By signing this consent form you agree to the collection and storage of blood, nasal and buccal samples for further pharmacogenomic analysis. Pharmacogenomics assesses how your specific genetic makeup handles a drug.

This form may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this sub-study. Before you decide to take part, you must understand the purpose of this optional sub-study, any potential risks to you, and what is expected of you during this sub-study. Even if you agree to participate in this optional sub-study you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING THE RESEARCH?

The company sponsoring this optional sub-study is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**NATURE AND PURPOSE**

When people are exposed to a substance or a mix of substances (e.g., food, smoke, drug), reactions in the body may be triggered. These reactions or responses will vary between each person, since each person has a different genetic material (genes).

Once the substance is absorbed by the body, it might affect the level of expression of these genes. These genes might then influence the time that some of the substances might remain in the body, how they are broken down or why some people might react differently to them.

Cells are the building blocks of the human body and each type of cell is specially adapted to its specific function in the body. All cells contain proteins that are produced from a substance called messenger ribonucleic acid (mRNA) and allow the cells to function.

The purpose of this sub-study is to collect the blood, nasal and buccal samples for analysis and investigations on how the smokers will respond to the aerosol (smoke) generated by the product THS 2.2, as compared to the subjects who are exposed to the smoke from conventional cigarettes, or as compared to a group of subjects who abstain from smoking ce).

The evaluation of these differences may provide insight into the biological processes that take place when using the study product as compared to conventional cigarettes or smoking abstinence. It will also allow us to compare if there are differences in the level of expression of these genes within a smoker between the mouth and the nose.

The samples will also be collected for determination of the quantity and quality of the RNA (pharmacogenomic) in blood samples to understand if the deleterious effect of smoking conventional cigarettes on cellular function could be decreased when switching to the test product or by smoking abstinence.

STUDY PROCEDURES

If you agree to participate in this sub-study, you will have the following three additional sample collection procedures:

Nasal epithelial collection ("collections of the cells from the nose") procedure (Day 0, Day 6 and Day 90)

You will be asked to blow your nose. This procedure will be performed on the left nostril only. If you wish to have the nostril numbed for the procedure, an anesthetic spray containing 1% Lidocaine will be used. A nasal speculum (device that resembles pliers) will be inserted to widen the left nostril, and then a soft brush will be inserted into the nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed. A second soft brush will be inserted into the same nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed.

Buccal sample collection ("collection of the cells from the mouth") procedure (Day 0, Day 6 and Day 90)

You will be asked to rinse out your mouth with water (about 4 teaspoons, 20 ml) that will be provided to you. A sterile brush will be inserted in your mouth and pushed slightly against the side of your mouth (inner cheek) until the shaft bends. The brush will be then rotated for about 10 seconds and the operation repeated with the other cheek.

**Blood collection for transcriptomics (Day 0, Day 6 and Day 91)**

Three additional blood samples for this type of analysis will be drawn (about 3 teaspoons, 15 ml in total). Specifically, one blood sample will be required from you at the beginning of the study on Day 0, a second blood sample on Day 6, and a third sample at the end of the study on Day 91.

STUDY PROCEDURE RISKS

During the collection of nasal and mouth samples, side effects that may occur include burning, pain, stinging, and nasal irritation. In rare cases, a nose bleed may occur. If you choose to have your nostrils to be numbed, the lidocaine spray may cause some allergic reactions and numbness. If misused, the lidocaine could cause serious side effects such as difficulty in breathing, swelling in the mouth or face and pain in the chest.

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

OTHER POTENTIAL RISKS

There are possible non-physical risks associated with this genetic research, such as the risks associated with a breach of privacy or confidentiality. Breach of confidentiality, may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to you or your family. Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

CONFIDENTIALITY

All of your samples will be given a code. This code will contain your age, sex, race, and other information. It will not contain your name or initials. As long as the samples are stored at the main study site they can be linked to you. Before samples are sent out from the main study site to an outside laboratory for analysis, they will be anonymized. This means that the link between you and the sample code will be deleted and there will be no possibility to trace the samples back to you. Anonymization is intended to prevent your re-identification.

The samples will be sent to the outside laboratory for analysis after all other data collected during the main study have been entered into a database (approximately 3-4 months after the last volunteer completed the study). As anonymized samples and associated data are not traceable back to you, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at your request if this is done after the samples are sent from the study site for analysis.

WITHDRAWAL OF SAMPLES

As explained above, it is your choice if you want to be in this sub-study. You can stop donating your biological samples at any time. Your decision to discontinue the participation to this sub-study does not impact your participation to the main study.



Your main study doctor will keep records that link your personal information with your coded samples until the shipment of the samples to an outside laboratory for analysis. Before the samples leave the study site the link will be deleted. If you withdraw your consent for the sub-study prior to deletion of this link, you may request your samples to be destroyed by the researchers and no longer used in research. If you withdraw your consent after the samples leave the study site, there will be no possibility to track them back to you and therefore it will be not possible to destroy them, or to exclude those samples from further analysis.

Sponsor and researchers working on its behalf shall be entitled to keep and use any research results that they obtain from your samples which were taken prior to your withdrawal of the consent.

BENEFITS

There is no direct benefit to you by taking part in this study. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor your study doctor will be contacted by the researchers in connection with the research or any information about the results of the tests performed on the samples from this sub-study.

ALTERNATIVE

You have the choice not to take part in this optional sub-study.

COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$150.00

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

WHO HAS REVIEWED THE STUDY?

MLIRB Independent Review Board has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 214-920-9053.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

**PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS**

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

**CONSENT AND SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

I have read the above information in a language, which I understand well. The content and meaning of this information has been explained to me.

I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacySignature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY
APR 28 2014
MLIRB
MLIRB
MLIRB

**INFORMED CONSENT DOCUMENT FOR GENETIC AND PHARMACOGENOMIC ANALYSIS**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	<u>Covance Daytona Beach Site</u> Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	<u>Covance Daytona Beach Site</u> 1900 Mason Avenue, Suite 140 Daytona Beach, FL, 32117
Telephone #:	<u>Covance Daytona Beach Site</u> Ph: 386-366-6400
24 hour Telephone #:	<u>Covance Daytona Beach Site</u> Ph: 386-366-6400
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

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intention of this document is to give you information so that you can decide if you want to participate to this optional sub-study.

You are being asked to allow the collection of a sample of your blood as well as nasal and buccal (from the mouth) samples. Genetic analysis will then be conducted on these samples. Having your samples drawn for this genetic research is voluntary. You do not have to agree to be in the genetic research study to take part in the main study.

Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this research sub-study. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given a copy of it to keep. If you do not agree to participate in the genetic research study, this does not prevent you from participating to the main study.

You must have reviewed and signed the main study informed consent before you review this consent form.

This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

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BUSINESS CONFIDENTIALITY

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

**NATURE AND PURPOSE**

When people are exposed to a substance or a mix of substances (e.g., food, smoke, drug), reactions in the body may be triggered. These reactions or responses will vary between each person, since each person has a different genetic material (genes).

Once the substance is absorbed by the body, it might affect the level of expression of these genes. These genes might then influence the time that some of the substances might remain in the body, how they are broken down or why some people might react differently to them.

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The purpose of this sub-study is to collect the blood, nasal and buccal samples for analysis and investigations on how the smokers will respond to the aerosol (smoke) generated by the product THS 2.2, as compared to the subjects who are exposed to the smoke from conventional cigarettes, or as compared to a group of subjects who abstain from smoking ce).

The evaluation of these differences may provide insight into the biological processes that take place when using the study product as compared to conventional cigarettes or smoking abstinence. It will also allow us to compare if there are differences in the level of expression of these genes within a smoker between the mouth and the nose.

The samples will also be collected for determination of the quantity and quality of the RNA (pharmacogenomic) in blood samples to understand if the deleterious effect of smoking conventional cigarettes on cellular function could be decreased when switching to the test product or by smoking abstinence.

STUDY PROCEDURES

If you agree to participate in this sub-study, you will have the following three additional sample collection procedures:

Nasal epithelial collection ("collections of the cells from the nose") procedure (Day 0, Day 6 and Day 90)

You will be asked to blow your nose. This procedure will be performed on the left nostril only. If you wish to have the nostril numbed for the procedure, an anesthetic spray containing 1% Lidocaine will be used. A nasal speculum (device that resembles pliers) will be inserted to widen the left nostril, and then a soft brush will be inserted into the nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed. A second soft brush will be inserted into the same nostril and pressed and rotated against the outside of the nostril for about 3 seconds, before being removed.

Buccal sample collection ("collection of the cells from the mouth") procedure (Day 0, Day 6 and Day 90)

You will be asked to rinse out your mouth with water (about 4 teaspoons, 20 ml) that will be provided to you. A sterile brush will be inserted in your mouth and pushed slightly against the side of your mouth (inner cheek) until the shaft bends. The brush will be then rotated for about 10 seconds and the operation repeated with the other cheek.

**Blood collection for transcriptomics (Day 0, Day 6 and Day 91)**

Three additional blood samples for this type of analysis will be drawn (about 3 teaspoons, 15 ml in total). Specifically, one blood sample will be required from you at the beginning of the study on Day 0, a second blood sample on Day 6 and a third sample at the end of the study on Day 91.

STUDY PROCEDURE RISKS

During the collection of nasal and mouth samples, side effects that may occur include burning, pain, stinging, and nasal irritation. In rare cases, a nose bleed may occur. If you choose to have your nostrils to be numbed, the lidocaine spray may cause some allergic reactions and numbness. If misused, the lidocaine could cause serious side effects such as difficulty in breathing, swelling in the mouth or face and pain in the chest.

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

OTHER POTENTIAL RISKS

There are possible non-physical risks associated with this genetic research, such as the risks associated with a breach of privacy or confidentiality. Breach of confidentiality, may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to you or your family. Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

CONFIDENTIALITY

All of your samples will be given a code. This code will contain your age, sex, race, and other information. It will not contain your name or initials. As long as the samples are stored at the main study site they can be linked to you. Before samples are sent out from the main study site to an outside laboratory for analysis, they will be anonymized. This means that the link between you and the sample code will be deleted and there will be no possibility to trace the samples back to you. Anonymization is intended to prevent your re-identification.

The samples will be sent to the outside laboratory for analysis after all other data collected during the main study have been entered into a database (approximately 3-4 months after the last volunteer completed the study). As anonymized samples and associated data are not traceable back to you, it is not possible to undertake actions such as sample withdrawal, or the return of individual results, even at your request if this is done after the samples are sent from the study site for analysis.

WITHDRAWAL OF SAMPLES

As explained above, it is your choice if you want to be in this sub-study. You can stop donating your biological samples at any time. Your decision to discontinue the participation to this sub-study does not impact your participation to the main study.



Your main study doctor will keep records that link your personal information with your coded samples until the shipment of the samples to an outside laboratory for analysis. Before the samples leave the study site the link will be deleted. If you withdraw your consent for the sub-study prior to deletion of this link, you may request your samples to be destroyed by the researchers and no longer used in research. If you withdraw your consent after the samples leave the study site, there will be no possibility to track them back to you and therefore it will be not possible to destroy them, or to exclude those samples from further analysis.

Sponsor and researchers working on its behalf shall be entitled to keep and use any research results that they obtain from your samples which were taken prior to your withdrawal of the consent.

BENEFITS

There is no direct benefit to you by taking part in this study. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor your study doctor will be contacted by the researchers in connection with the research or any information about the results of the tests performed on the samples from this sub-study.

ALTERNATIVE

You have the choice not to take part in this optional sub-study.

COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$150.00

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

WHO HAS REVIEWED THE STUDY?

MLIRB Independent Review Board has reviewed the objectives and the proposed conduct of the main study.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 386-366-6400.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

**PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS**

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the Midlands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the Midlands IRB at the number above or you can go to the Midlands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI at 386-366-6400.

LEGAL RIGHTS

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CONSENT AND SIGNATURES

Please read the following paragraph out loud to the person obtaining the consent.

I have read the above information in a language, which I understand well. The content and meaning of this information has been explained to me.

I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy

Signature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY
APR 28 2014
MLIRB
Medicine Learning and Research Board

Version#: 3
Approved by MLIRB on 04/28/14
Protocol#: ZRHM-REXA-08-US



**16.1.3.18.3 INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**

**INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in the "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This informed consent form tells you about "Optional Long-Term Storage (Bio-banking) of Plasma, Serum and Urine Samples for Further Biomarker of exposure/Risk Marker Research" (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study informed consent form that you have already signed.

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US



Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood and urine samples for further biomarker/risk marker analysis. If you do not agree to participate in this sub-study, this does not prevent you from participating to the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the optional research. This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional biomarker of exposure /risk marker analysis, any potential risks to you, and what is expected of you during procedures of this optional research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The company sponsoring this optional assessment is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

PURPOSE

The intention of this document is to ask your consent for collection of blood samples, and further long-term storage of resulting samples of plasma and serum (the different blood fractions) as well as for collection and long-term storage of urine samples. In addition, this informed consent documents asks for your permission to use these samples for further analysis of biological markers and of the risks of using the THS 2.2 product as compared to conventional cigarettes. .

These analyses will not include genetic testing done on your samples.

STUDY PROCEDURES

If you agree to participate in this sub-study, a blood sample will be obtained on Days 0, 6 and 90, of the main study (approximately 10 ml per blood draw, 30 ml in total (2 tablespoons), and you will have urine taken from your main study urine collection that starts on Day 0, Day 5 and Day 90 (10 tubes of urine per time point, 30 tubes in total; approximately 300 ml of urine in total).

**STUDY PROCEDURE RISKS**

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

BENEFITS

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding why people react differently to products that contain tobacco.

ALTERNATIVE

Your alternative is to not participate in this sub-study.

SAMPLE ANALYSIS AND STORAGE

Your plasma, serum and urine samples will be shipped for long-term storage and analysis to laboratories contracted by the Sponsor (Philip Morris Products S.A.) which have experience in analyzing as well as storing of such samples.

The samples will be destroyed when the maximum storage time has been reached (5 years for plasma and urine samples, and 2 years for urine samples) or no further analyses are possible (whichever is earlier). You should be aware that Philip Morris Products S.A. might not conduct all research immediately and that your samples may be studied at any time before they are destroyed.

WITHDRAWAL OF SAMPLES

You can stop any further analysis of your samples at any time. Tell the study doctor if you no longer want to be in this sub-study.

If you withdraw your consent for further storage / analysis of your samples, you may request your plasma, serum and urine samples to be destroyed and no longer used in the research. However, the Sponsor shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

CONFIDENTIALITY

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. All the samples will be given a code. This code will contain your age, sex, race, and other information. Your plasma, serum and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. However using the sample code, Investigator or study staff can link the samples to you.

Sponsor may use other laboratories, investigators, commercial or academic third parties as Sponsor's "agents" to assist in this research. All such individuals are required to keep the data confidential.

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

**BUSINESS CONFIDENTIALITY**

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited

WHAT WILL HAPPEN WITH THE RESULTS OF THIS OPTIONAL RESEARCH?

You will not be provided with any information about the results of this optional biomarker research. You will also not be given any information about the results of the optional research that may relate to your personal health. Although you have the right to access information in your medical records, the information that the Sponsor will maintain in their databases and create during biomarker of exposure/risk marker analysis is for research purposes only. The Sponsor will not return any biomarker of exposure/risk marker analysis information to you or the main study investigator. Information resulting from the research will not be entered into your medical records. At some point, information about the results of the research may be published; however, you will not be notified of that publication. You will also not be personally identified in any such publication.

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

You will not have to pay for any analyses related to this optional research.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 214-920-9053

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

WHO HAS REVIEWED THE RESEARCH?

MidLands Independent Review Board has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favorable opinion of it.

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

**COMPENSATION FOR BEING IN THIS STUDY**

Total compensation for this optional sub-study will be \$100.00. You will receive this compensation together with the compensation for your participation to the main study.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. William Lewis at 214-920-9053.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

**CONSENT AND SIGNATURES****Please read the following paragraph out loud to the person obtaining the consent.**

I have read the above information, which is in a language that I understand well. The content and meaning of this information has been explained to me.

I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

APPROVED BY
JUL 02 2013
MLIRB
Multinational Independent Review Board

**INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1900 Mason Avenue, Suite 140 Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 972-955-6373
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in the "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This informed consent form tells you about "Optional Long-Term Storage (Bio-banking) of Plasma, Serum and Urine Samples for Further Biomarker of exposure/Risk Marker Research" (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study informed consent form that you have already signed.

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US



Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood and urine samples for further biomarker/risk marker analysis. If you do not agree to participate in this sub-study, this does not prevent you from participating to the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the optional research. This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional biomarker of exposure /risk marker analysis, any potential risks to you, and what is expected of you during procedures of this optional research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The company sponsoring this optional assessment is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

PURPOSE

The intention of this document is to ask your consent for collection of blood samples, and further long-term storage of resulting samples of plasma and serum (the different blood fractions) as well as for collection and long-term storage of urine samples. In addition, this informed consent documents asks for your permission to use these samples for further analysis of biological markers and of the risks of using the THS 2.2 product as compared to conventional cigarettes.

These analyses will not include genetic testing done on your samples.

STUDY PROCEDURES

If you agree to participate in this sub-study, a blood sample will be obtained on Days 0, 6 and 90, of the main study (approximately 10 ml per blood draw, 30 ml in total (2 tablespoons), and you will have urine taken from your main study urine collection that starts on Day 0, Day 5 and Day 90 (10 tubes of urine per time point, 30 tubes in total; approximately 300 ml of urine in total).

**STUDY PROCEDURE RISKS**

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

BENEFITS

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding why people react differently to products that contain tobacco.

ALTERNATIVE

Your alternative is to not participate in this sub-study.

SAMPLE ANALYSIS AND STORAGE

Your plasma, serum and urine samples will be shipped for long-term storage and analysis to laboratories contracted by the Sponsor (Philip Morris Products S.A.) which have experience in analyzing as well as storing of such samples.

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WITHDRAWAL OF SAMPLES

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If you withdraw your consent for further storage / analysis of your samples, you may request your plasma, serum and urine samples to be destroyed and no longer used in the research. However, the Sponsor shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

CONFIDENTIALITY

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. All the samples will be given a code. This code will contain your age, sex, race, and other information. Your plasma, serum and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. However using the sample code, Investigator or study staff can link the samples to you.

Sponsor may use other laboratories, investigators, commercial or academic third parties as Sponsor's "agents" to assist in this research. All such individuals are required to keep the data confidential.

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

**BUSINESS CONFIDENTIALITY**

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHAT WILL HAPPEN WITH THE RESULTS OF THIS OPTIONAL RESEARCH?

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DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

You will not have to pay for any analyses related to this optional research.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 386-366-6400.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

WHO HAS REVIEWED THE RESEARCH?

MidLands Independent Review Board has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favorable opinion of it.

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US



COMPENSATION FOR BEING IN THIS STUDY

Total compensation for this optional sub-study will be \$100.00. You will receive this compensation together with the compensation for your participation to the main study.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr., at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

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CONSENT AND SIGNATURES

Please read the following paragraph out loud to the person obtaining the consent.

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I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy

Signature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

Version#: 1

Approved by MLIRB on 07/02/13

Protocol#: ZRHM-REXA-08-US

APPROVED BY
JUL 02 2013
MLIRB
Multimedia Independent Review Board

**INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Dallas Site Dr. William Lewis
Research Site Address:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Telephone #:	Covance Dallas Site Ph: 214-920-9053
24 hour Telephone #:	Covance Dallas Site Ph: 972-955-5373
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in the "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This informed consent form tells you about "Optional Long-Term Storage (Bio-banking) of Plasma, Serum and Urine Samples for Further Biomarker of exposure/Risk Marker Research" (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study informed consent form that you have already signed.

Version#: 2

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US



Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood and urine samples for further biomarker/risk marker analysis. If you do not agree to participate in this sub-study, this does not prevent you from participating to the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the optional research. This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional biomarker of exposure /risk marker analysis, any potential risks to you, and what is expected of you during procedures of this optional research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The company sponsoring this optional assessment is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

PURPOSE

The intention of this document is to ask your consent for collection of blood samples, and further long-term storage of resulting samples of plasma and serum (the different blood fractions) as well as for collection and long-term storage of urine samples. In addition, this informed consent documents asks for your permission to use these samples for further analysis of biological markers and of the risks of using the THS 2.2 product as compared to conventional cigarettes. .

These analyses will not include genetic testing done on your samples.

STUDY PROCEDURES

If you agree to participate in this sub-study, a blood sample will be obtained on Days 0, 6 and 91, of the main study (approximately 10 ml per blood draw, 30 ml in total (2 tablespoons), and you will have urine taken from your main study urine collection that starts on Day 0, Day 5 and Day 90 (10 tubes of urine per time point, 30 tubes in total; approximately 300 ml of urine in total).

**STUDY PROCEDURE RISKS**

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

BENEFITS

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding why people react differently to products that contain tobacco.

ALTERNATIVE

Your alternative is to not participate in this sub-study.

SAMPLE ANALYSIS AND STORAGE

Your plasma, serum and urine samples will be shipped for long-term storage and analysis to laboratories contracted by the Sponsor (Philip Morris Products S.A.) which have experience in analyzing as well as storing of such samples.

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Version#: 2

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US

**BUSINESS CONFIDENTIALITY**

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

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You will not be provided with any information about the results of this optional biomarker research. You will also not be given any information about the results of the optional research that may relate to your personal health. Although you have the right to access information in your medical records, the information that the Sponsor will maintain in their databases and create during biomarker of exposure/risk marker analysis is for research purposes only. The Sponsor will not return any biomarker of exposure/risk marker analysis information to you or the main study investigator. Information resulting from the research will not be entered into your medical records. At some point, information about the results of the research may be published; however, you will not be notified of that publication. You will also not be personally identified in any such publication.

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WHO HAS REVIEWED THE RESEARCH?

MidLands Independent Review Board has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favorable opinion of it.

Version#: 2

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Protocol#: ZRHM-REXA-08-US

**COMPENSATION FOR BEING IN THIS STUDY**

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If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. William Lewis at 214-920-9053.

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I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.

I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.

I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name_____
Participant Signature_____
Date_____
Time_____
Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Signature of Person
conducting the Informed
Consent discussion
and verification of literacy_____
Date_____
Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature_____
Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY
APR 14 2014
MLIRB
Multinational Independent Review Board

Version#: 2

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US

**INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Protocol: ZRHM-REXA-08-US

Subject's screening number:	<input type="text"/>
Principal Investigator: (Study Doctor)	Covance Daytona Beach Site Dr. H. Frank Farmer, Jr., M.D., Ph.D., FACP, CPI
Research Site Address:	Covance Daytona Beach Site 1900 Mason Avenue, Suite 140 Daytona Beach, FL 32117
Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
24 hour Telephone #:	Covance Daytona Beach Site Ph: 386-366-6400
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

INTRODUCTION

You have already agreed to participate in the "Reduced exposure study using THS 2.2" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new Modified Risk Tobacco Product, on selected biological markers (biomarkers) of exposure compared to normal (conventional) cigarettes.

This informed consent form tells you about "Optional Long-Term Storage (Bio-banking) of Plasma, Serum and Urine Samples for Further Biomarker of exposure/Risk Marker Research" (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study informed consent form that you have already signed.

Version#: 2

Approved by MLIRB on 12/13/13

Protocol#: ZRHM-REXA-08-US



Your study doctor or study staff will explain all the procedures and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood and urine samples for further biomarker/risk marker analysis. If you do not agree to participate in this sub-study, this does not prevent you from participating to the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the optional research. This form is not meant to replace the one for the main study, and the contents of the main study informed consent form explain the overall purpose of this research and the conditions for your participation in the main study.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional biomarker of exposure /risk marker analysis, any potential risks to you, and what is expected of you during procedures of this optional research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The company sponsoring this optional assessment is Philip Morris Products S.A., Switzerland (including agents, contractors or consultants). Philip Morris Products S.A. is a manufacturer of tobacco products. As explained in the main study informed consent, the Sponsor is developing an alternative approach to the conventional (normal) cigarettes, by developing a product which may have the potential to reduce some of the risks of tobacco-related diseases.

PURPOSE

The intention of this document is to ask your consent for collection of blood samples, and further long-term storage of resulting samples of plasma and serum (the different blood fractions) as well as for collection and long-term storage of urine samples. In addition, this informed consent documents asks for your permission to use these samples for further analysis of biological markers and of the risks of using the THS 2.2 product as compared to conventional cigarettes. .

These analyses will not include genetic testing done on your samples.

STUDY PROCEDURES

If you agree to participate in this sub-study, a blood sample will be obtained on Days 0, 6 and 90, of the main study (approximately 10 ml per blood draw, 30 ml in total (2 tablespoons), and you will have urine taken from your main study urine collection that starts on Day 0, Day 5 and Day 90 (10 tubes of urine per time point, 30 tubes in total; approximately 300 ml of urine in total).

**STUDY PROCEDURE RISKS**

During the collection of blood samples, you may experience pain and/or bruising at the insertion site of the needle/catheter or location of the blood pressure cuff. Although rare, localized clot formation, nerve damage and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The potential risks of participating in the main study are described in the main study informed consent document.

BENEFITS

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding why people react differently to products that contain tobacco.

ALTERNATIVE

Your alternative is to not participate in this sub-study.

SAMPLE ANALYSIS AND STORAGE

Your plasma, serum and urine samples will be shipped for long-term storage and analysis to laboratories contracted by the Sponsor (Philip Morris Products S.A.) which have experience in analyzing as well as storing of such samples.

The samples will be destroyed when the maximum storage time has been reached (5 years for plasma and urine samples, and 2 years for urine samples) or no further analyses are possible (whichever is earlier). You should be aware that Philip Morris Products S.A. might not conduct all research immediately and that your samples may be studied at any time before they are destroyed.

WITHDRAWAL OF SAMPLES

You can stop any further analysis of your samples at any time. Tell the study doctor if you no longer want to be in this sub-study.

If you withdraw your consent for further storage / analysis of your samples, you may request your plasma, serum and urine samples to be destroyed and no longer used in the research. However, the Sponsor shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

CONFIDENTIALITY

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. All the samples will be given a code. This code will contain your age, sex, race, and other information. Your plasma, serum and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. However using the sample code, Investigator or study staff can link the samples to you.

Sponsor may use other laboratories, investigators, commercial or academic third parties as Sponsor's "agents" to assist in this research. All such individuals are required to keep the data confidential.

Version#: 2

Approved by MLIRB on 12/13/13

Protocol#: ZRHM-REXA-08-US

**BUSINESS CONFIDENTIALITY**

The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHAT WILL HAPPEN WITH THE RESULTS OF THIS OPTIONAL RESEARCH?

You will not be provided with any information about the results of this optional biomarker research. You will also not be given any information about the results of the optional research that may relate to your personal health. Although you have the right to access information in your medical records, the information that the Sponsor will maintain in their databases and create during biomarker of exposure/risk marker analysis is for research purposes only. The Sponsor will not return any biomarker of exposure/risk marker analysis information to you or the main study investigator. Information resulting from the research will not be entered into your medical records. At some point, information about the results of the research may be published; however, you will not be notified of that publication. You will also not be personally identified in any such publication.

DEVELOPMENT FOR COMMERCIAL GAIN

Although future research that uses your samples may lead to the development of new products, you will not receive any compensation for these new products. By agreeing to this research, you are giving up all claims to any money obtained by the researchers from commercial or other use of these specimens.

You will not have to pay for any analyses related to this optional research.

IN CASE OF INJURY

Your safety is the major concern of every member of the study staff. Please contact the study staff as soon as possible if you have side effects or injuries. Their phone number is 386-366-6400.

The study staff will provide immediate medical treatment, without cost to you, for side effects or injuries caused by being in this study. Other than the costs of immediate medical treatment, your medical expenses for any research-related injury will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

WHO HAS REVIEWED THE RESEARCH?

Midlands Independent Review Board has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favorable opinion of it.

Version#: 2

Approved by MLIRB on 12/13/13

Protocol#: ZRHM-REXA-08-US

**COMPENSATION FOR BEING IN THIS STUDY**

Total compensation for this optional sub-study will be \$100.00. You will receive this compensation together with the compensation for your participation to the main study.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr., at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

LEGAL RIGHTS

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**CONSENT AND SIGNATURES**

Please read the following paragraph out loud to the person obtaining the consent.

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Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
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I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

Version#: 2

Approved by MLIRB on 12/13/13

Protocol#: ZRHM-REXA-08-US

APPROVED BY
DEC 13 2013
MLIRB
Monitored Independent Review Board

**INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**

Study Title. A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

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Subject's screening number:	<input type="text"/>
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Version#: 3

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US



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The information and any materials or items that you are given about or during the study, such as information identifying the research unit, the sponsor, any study product(s), and/or the type of study being performed - should be considered confidential business information of Covance and the study sponsor. You are of course free to discuss such information under confidence with others, such as your doctor or with your friends and family, for purposes of considering whether to participate in this study or at any time when discussing your present or future healthcare or rights. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

WHAT WILL HAPPEN WITH THE RESULTS OF THIS OPTIONAL RESEARCH?

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WHO HAS REVIEWED THE RESEARCH?

Midlands Independent Review Board has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favorable opinion of it.

Version#: 3

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US

**COMPENSATION FOR BEING IN THIS STUDY**

Total compensation for this optional sub-study will be \$100.00. You will receive this compensation together with the compensation for your participation to the main study.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have any questions or problems during this study, if you think that you may have experienced a research-related injury, or if you have questions about the availability of medical care, you should contact Dr. H. Frank Farmer, Jr., at 386-366-6400.

If you have questions about your rights, general questions, complaints or concerns about this research, or questions about your rights as a person taking part in this study, call the MidLands Independent Review Board (MLIRB) at (913) 385-1414 or (800) 636-4445. If, at any time during or after your participation in this research, you would like information or to offer input about your research experience, you can call the MidLands IRB at the number above or you can go to the MidLands IRB website at www.mlirb.com and give us your comments. Either way, you do not have to give us your name, if you do not want to.

You have the right to ask any questions concerning the potential and/or unknown hazards of this study, at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, contact Dr. H. Frank Farmer, Jr. at 386-366-6400.

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**CONSENT AND SIGNATURES**

Please read the following paragraph out loud to the person obtaining the consent.

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I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study.
I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this sub-study.
I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.
I voluntarily and freely donate any and all biological samples for the research described above and hereby relinquish all property rights, title, and interest I may have in those samples.

Print Participant Name

Participant Signature

Date

Time

Print Name of Person
conducting the Informed
Consent discussion
and verification of literacy

Signature of Person
conducting the Informed
Consent discussion
and verification of literacy

Date

Time

I have received a copy of this signed and dated study consent form to keep.

Your Signature

Date

To be completed by Covance Staff Only:

QC'd by _____

Date _____

APPROVED BY
APR 14 2014
MLIRB
Covance Independent Review Board

Version#: 3

Approved by MLIRB on 04/14/14

Protocol#: ZRHM-REXA-08-US



16.1.3.19 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM (LOCAL LANGUAGE)

16.1.3.19.1 MAIN INFORMED CONSENT FORM

**AUTORIZACIÓN Y CONSENTIMIENTO INFORMADO PARA PARTICIPAR
EN UNA INVESTIGACIÓN CLÍNICA**

Título del estudio: Estudio aleatorizado, controlado, abierto, multicéntrico, de 3 grupos paralelos, para demostrar las reducciones en la exposición a constituyentes del humo seleccionados en fumadores aparentemente sanos que cambian al sistema de calentamiento de tabaco mentolado 2.2 (THS 2.2 Menthol) o dejan de fumar, en comparación con continuar usando cigarrillos mentolados convencionales, durante 5 días en internamiento y 86 días más en un contexto ambulatorio.

Protocolo: ZRHM-REXA-08-US

Número de selección del sujeto	<input type="text"/>
Investigador principal: (médico del estudio)	Covance Dallas Site Dr. William Lewis
Dirección del centro de investigación:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Número de teléfono:	Covance Dallas Site Teléfono: 214-920-9053
Número de teléfono las 24 horas:	Covance Dallas Site Teléfono: 972-955-5373
Patrocinador:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Suiza

Se le invita a participar en un estudio de investigación. Sin embargo, antes de que dé su consentimiento para participar en el estudio, lea lo siguiente y haga todas las preguntas que sean necesarias para asegurarnos de que comprende qué implicará su participación. Se le entregará una copia de este formulario de consentimiento informado para que se la lleve a su casa.

Fecha: 30 de enero de 2014

Versión n.º 4

Aprobado por MLIRB el 1/14/2014

Protocolo n.º ZRHM-REXA-08-US

Página 1 de 36



INTRODUCCIÓN

Su participación en este estudio de investigación es voluntaria. Es importante que lea y comprenda la siguiente explicación de los procedimientos propuestos. Este formulario de consentimiento informado describe el objetivo, los procedimientos, los beneficios, las alternativas, los riesgos conocidos o reconocidos, las molestias y las precauciones del estudio, e incluye la duración y la naturaleza de su participación. También describe su derecho a retirarse del estudio en cualquier momento. Para ingresar en el estudio, debe firmar y fechar este formulario de consentimiento en calidad de participante de la investigación.

Tenga en cuenta lo siguiente: si no es absolutamente sincero con el médico respecto a sus antecedentes de salud, que incluyen alergias y uso de medicamentos, podría perjudicarse al participar en este estudio.

NATURALEZA Y OBJETIVO DEL ESTUDIO

El patrocinador de este estudio es Philip Morris Products, un fabricante de productos que contienen tabaco. El patrocinador está desarrollando un enfoque alternativo a los cigarrillos convencionales (normales) a través de un producto que posiblemente permita reducir algunos riesgos de las enfermedades relacionadas con el tabaco.

El sistema de calentamiento de tabaco mentolado 2.2 (*tobacco heating system*, THS 2.2 Menthol) es un producto en fase de investigación que se está desarrollando como una alternativa en lugar de los cigarrillos convencionales que no ha sido aprobada por la Administración de Alimentos y Medicamentos (*Food and Drug Administration*, FDA) de los Estados Unidos.

Se cree que al calentar el tabaco, en lugar de quemarlo como ocurre con los cigarrillos convencionales, es posible que se reduzcan los efectos perjudiciales de fumar.

No se ha demostrado que el producto THS 2.2 Menthol reduzca las enfermedades relacionadas con el consumo de tabaco y usted no debe suponer que los riesgos asociados al uso del producto THS 2.2 Menthol sean diferentes de los que produce fumar cigarrillos comunes.

El objetivo general de este estudio es reunir información sobre el uso del producto en fase de investigación THS 2.2 Menthol cuando se proporciona a los participantes de una investigación que están hospitalizados en el centro de investigación y luego en un contexto ambulatorio. El estudio de investigación comparará el uso del producto THS 2.2 Menthol con los cigarrillos mentolados convencionales y la abstinencia de fumar. Durante este estudio se medirán varios biomarcadores de exposición presentes en el cuerpo y marcadores de riesgo. El estudio también obtendrá información de seguridad relacionada con el uso del producto THS 2.2 Menthol.

Los biomarcadores de exposición son sustancias que se miden en el cuerpo como el resultado del consumo de otra sustancia (como el humo de cigarrillo). Por ejemplo,

Fecha: 30 de enero de 2014

Versión n.º 4

Aprobado por MLIRB el 1/14/2014

Protocolo n.º ZRHM-REXA-08-US

Página 2 de 36



cuando fuma usted inhala monóxido de carbono. El monóxido de carbono se une a determinada parte de los glóbulos rojos llamada hemoglobina. El monóxido de carbono puede reemplazar al oxígeno presente en los glóbulos rojos. En este estudio, se medirá el nivel de monóxido de carbono unido a la hemoglobina y se hará referencia a este nivel como un biomarcador de exposición al monóxido de carbono.

Un marcador de riesgo es una característica biológica que se asocia a un mayor riesgo de desarrollar determinadas enfermedades o infecciones. Para comprender las diferencias biológicas (fisiológicas) entre el producto THS 2.2 Menthol, los cigarrillos mentolados convencionales y la abstinencia de fumar, se tomarán otras mediciones, incluidos los marcadores de irritación (inflamación) de la nariz y de los tipos de colesterol en la sangre.

Los objetivos adicionales de este estudio de investigación son comprender mejor lo que el cuerpo hace con la nicotina y sus productos de degradación (incluidas las enzimas que intervienen en la degradación) en los fumadores que cambian de cigarrillos mentolados convencionales al producto THS 2.2 Menthol en comparación con los fumadores que continúan fumando cigarrillos mentolados convencionales. Además, en este estudio se evaluarán los patrones y las preferencias del hábito de fumar (es decir, la topografía del fumador), el uso del producto y los efectos subjetivos relacionados.

Este estudio tiene solamente fines de investigación y no está destinado a tratar ningún problema médico.

También se le invitará a participar en dos subestudios adicionales, opcionales. En uno, se realizarán análisis farmacogenómicos de sus muestras biológicas. No está obligado a participar en ninguno de estos dos subestudios opcionales. Se le entregarán 2 formularios de consentimiento informado separados para estos subestudios adicionales. **Si no desea participar en estos subestudios adicionales, su participación en este estudio de investigación principal no se verá afectada.**

Covance Clinical Research Unit Inc. recibe un pago por evaluar el producto en fase de investigación THS 2.2 Menthol. Los médicos de este estudio trabajan para Covance, pero no tienen ningún interés económico en los resultados de este estudio.

¿QUÉ PRODUCTO SE ESTÁ EVALUANDO?

El producto que desarrolla el patrocinador y que se evalúa en este estudio se llama THS 2.2 Menthol. Este producto mantiene el calentamiento del tabaco a una temperatura mucho más baja que la que se observa en los cigarrillos normales (convencionales). El producto THS 2.2 Menthol consta de los siguientes componentes: las ramas de tabaco mentolado para el THS (ramas de tabaco mentolado), la boquilla, el cargador, una herramienta para limpieza, una fuente de energía principal y un cable USB.

El dispositivo de calentamiento de tabaco comprende todos estos componentes en el producto THS 2.2 Menthol, excepto las ramas de tabaco mentolado. La función de la

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boquilla es calentar la rama de tabaco mentolado, lo que produce un aerosol que recibe el usuario. El calentamiento eléctrico funciona con una batería interna que genera energía durante aproximadamente 6 minutos (lo que alcanza para el uso completo de una sola rama de tabaco). A diferencia de los cigarrillos normales, las ramas de tabaco mentolado no se queman durante el consumo y el largo sigue siendo el mismo después de su uso.

En este momento, es importante que usted comprenda que no se ha demostrado que el producto THS 2.2 Menthol reduzca las enfermedades relacionadas con el tabaco y no debe suponer que los riesgos asociados con el uso de este producto sean diferentes de los que se relacionan con fumar cigarrillos normales.

SELECCIÓN DE LOS PARTICIPANTES DE LA INVESTIGACIÓN

Se le invita a participar en este estudio porque usted es una fumadora o un fumador aparentemente sano que tiene más de 22 años de edad y fuma cigarrillos mentolados convencionales, y posiblemente sea apto para participar en este estudio.

Si está pensando seriamente en dejar de fumar en los próximos 6 meses, usted no califica para participar en este estudio. Sin embargo, debe estar dispuesto(a) a abstenerse de fumar durante el estudio si resulta seleccionado al azar para el grupo de abstinencia del tabaco.

Si es una mujer, no debe estar embarazada ni amamantando. Si decide participar en este estudio, se le pedirá que use métodos anticonceptivos adecuados durante el estudio.

Es importante que responda completamente y con sinceridad todas las preguntas de selección. Debe comunicar todas las enfermedades y alergias actuales y anteriores, así como todos los medicamentos que esté usando, incluidos los medicamentos recetados y de venta libre. **Si no revela toda la información sobre sus antecedentes médicos, cualquier problema médico que usted tenga y los medicamentos que ha usado, podría ser peligroso para su salud.**

En este estudio de investigación multicéntrico, se asignarán de forma aleatoria 160 participantes.

DURACIÓN DEL ESTUDIO

La duración de su participación en este estudio es de aproximadamente 123 a 150 días incluido el período de selección. Se realizará una visita de selección como máximo 28 días (día -30 a día -3) antes de la admisión en el centro de investigación (para determinar si usted reúne los requisitos para este estudio de investigación). Este estudio requiere un internamiento de 9 días y 8 noches (día -2 a día 6) en el centro de investigación seguida de 3 visitas los días 30 a 31, 60 a 61 y 90 a 91. Cada visita constará de 2 días consecutivos (con estadía de 1 noche en cada visita) en el centro. En la visita del día 30, ingresará al centro antes de las 8:30 a. m. y saldrá después de

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que se hayan realizado todas las evaluaciones del día 31. En la visita del día 60, ingresará al centro antes de las 8:30 a. m. del día 60 y saldrá después de que se hayan realizado todas las evaluaciones del día 61. En la visita del día 90, ingresará al centro antes de las 8:30 a. m. del día 90 y será dado de alta el día 91, después de que se hayan realizado todas las evaluaciones.

Después del día 91, habrá un período de seguimiento de seguridad de 28 días durante el cual debe comunicarle al personal del centro cualquier problema médico nuevo que tenga. El personal del centro también se comunicará con usted para realizar un seguimiento de cualquier problema médico que usted comunique durante el estudio o durante el período de seguimiento que no se haya resuelto después de haber sido dado de alta del centro, el día 91.

Durante el estudio, desde la selección hasta la finalización del período de seguimiento de seguridad, siempre debe comunicarse con el centro antes de tomar cualquier medicamento (recetado o de venta libre).

DISEÑO DEL ESTUDIO

Este estudio de investigación será de “diseño abierto”. Esto significa que usted, el médico del estudio y el patrocinador sabrán qué productos recibe. Una vez que se determine que usted reúne los requisitos para el estudio, será asignado de forma aleatoria (al azar, como cuando se arroja una moneda al aire) a 1 de los siguientes 3 grupos del estudio. Esto se realizará el día 0. El día 1, se le comunicará el grupo al cual fue asignado. Usted no podrá elegir el grupo al cual es asignado.

Usted tiene un 50% de probabilidades de estar en el grupo 1 y un 25% de estar en el grupo 2 o 3.

- **Grupo 1:** grupo del sistema de calentamiento de tabaco, THS 2.2 Menthol (80 participantes).
- **Grupo 2:** grupo de cigarrillos mentolados convencionales (40 participantes).
- **Grupo 3:** grupo de abstinencia de fumar (40 participantes).

Si es asignado al grupo 1 o 2, se le permitirá fumar durante el período de internamiento (desde el día 1 hasta el momento en que sea dado de alta del centro, el día 6) entre las 6:30 a. m. y las 11:00 p. m. cada día. Durante este período, usted puede usar la cantidad de ramas de tabaco del producto THS 2.2 Menthol que desee si está en el grupo 1 o fumar la cantidad de cigarrillos mentolados convencionales que desee si está en el grupo 2. Sin embargo, no tendrá libre acceso a los cigarrillos mentolados convencionales ni al producto THS 2.2 Menthol. El personal del estudio distribuirá los cigarrillos mentolados convencionales y las ramas de tabaco del producto THS 2.2 Menthol cuando usted lo solicite, uno a la vez. No está permitido fumar durante la realización de los procedimientos del estudio. El día 6, no podrá fumar ni usar el producto THS 2.2 Menthol antes de que se hayan realizado todos los análisis de laboratorio y todas las pruebas para evaluar la función pulmonar completa. En este estudio no se permite fumar fuera del edificio, por lo tanto, se le pedirá que fume sus

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cigarillos mentolados convencionales o que use el producto THS 2.2 Menthol en una cabina para fumar dentro del edificio. La cabina está construida en vidrio y tiene espacio para 8 personas a la vez. La cabina utiliza filtros para contener el humo y evitar que salga de allí. Un miembro del personal le explicará cómo usar las cabinas y cómo apagar sus cigarillos mentolados convencionales o desechar las ramas de tabaco del THS 2.2 Menthol cuando haya terminado de usarlas o de fumar.

Si es asignado al grupo 3, se requiere abstinencia completa de fumar durante todo el estudio, desde el día 1 hasta el día 91. Durante el período de internamiento que abarca desde el día 1 hasta el día 6, el personal del centro supervisará cuidadosamente a todos los participantes de la investigación del grupo 3 para detectar posibles signos y síntomas de la abstinencia de nicotina. Durante este período, no puede usar ningún medicamento para ayudar a la abstinencia de fumar ni usar ningún producto que contenga tabaco/nicotina. Se le brindará ayuda psicológica durante el período de abstinencia de fumar.

Al final del período de internamiento cuando usted sea dado de alta del centro el día 6, se le indicará que continúe con el producto/régimen al cual fue asignado en un contexto ambulatorio durante 86 días; esto es, continuar usando el producto THS 2.2 Menthol, si fue asignado al grupo 1, y continuar fumando los cigarillos mentolados convencionales, si fue asignado al grupo 2; o bien, abstenerse de fumar, si fue asignado al grupo 3. Tendrá que registrar todos los días en un diario electrónico cualquier uso del producto THS 2.2 Menthol, cigarillos convencionales (mentolados o no mentolados), terapia de reemplazo de la nicotina, por ejemplo, goma de mascar de nicotina u otros productos que contengan nicotina/tabaco. Si durante el período ambulatorio usa cualquier otro producto que contenga nicotina/tabaco distinto del producto/régimen asignado, no se le pedirá que deje de participar en el estudio.

Durante el período ambulatorio, no habrá restricciones con respecto a fumar/al uso del producto, excepto durante las tres visitas al centro (visitas de los días 30, 60 y 90), cuando se permitirá el uso del producto desde el ingreso por la mañana antes de las 8:30 a. m. hasta las 11:00 p. m. de los días 30, 60 y 90. Los días 31 y 61, se permitirá el uso del producto desde las 6:30 a. m. en adelante. El día 91, se permitirá el uso del producto después de que se hayan realizado algunas evaluaciones (por ejemplo, la Escala Minnesota de abstinencia de la nicotina [*Minnesota Nicotine Withdrawal Scale*] y cuestionarios sobre la tos, evaluaciones de la función pulmonar completa) hasta el momento del alta del día 91. Si fue asignado al grupo de cigarillos mentolados convencionales o el grupo de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol.

Si fue asignado al grupo del producto THS 2.2 Menthol, el personal del centro le dará instrucciones sobre cómo desechar las ramas de tabaco del producto THS Menthol.

Si es asignado al grupo 1 (grupo del producto THS 2.2 Menthol), durante el período ambulatorio tendrá que visitar el centro aproximadamente cada 2 semanas para que se le suministren nuevos paquetes de ramas de tabaco del producto THS 2.2 Menthol. Durante esta visita no se realizará ninguna otra evaluación. Cuando venga a la clínica

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para las visitas de los días 30, 60 y 90, deberá devolver al centro los paquetes vacíos, sin usar y abiertos de las ramas de tabaco del producto THS 2.2 Menthol sin usar, así como las piezas del producto THS 2.2 Menthol (es decir, las ramas de tabaco del THS, la boquilla, el cargador y los accesorios del THS).

Si en cualquier momento durante el estudio desea dejar de fumar, el personal del estudio le ayudará con esta decisión y lo referirá a los servicios médicos. Permanecerá en el estudio y completará las visitas y los procedimientos restantes. Sin embargo, puede decidir retirarse del estudio en cualquier momento.

SELECCIÓN

Acudirá a la clínica para una visita de selección en la que se determinará si usted es elegible para participar en este estudio. La visita de selección tendrá lugar como máximo 28 días antes de la admisión en el centro. Se espera que llegue al centro de investigación habiendo ayunado durante al menos 10 horas, que se requiere para determinados análisis de sangre. Antes de que se realicen las pruebas y los procedimientos relacionados con el estudio, se le pedirá que lea y firme este documento de consentimiento. Para determinar si reúne los requisitos para participar en este estudio, se llevarán a cabo las pruebas y los procedimientos siguientes:

- Se le asesorará sobre el riesgo de fumar (entrevista breve de conformidad con las recomendaciones del Servicio de Salud Pública [*Public Health Service*] de los Estados Unidos), y se le brindará asesoramiento para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se reunirá información demográfica sobre usted (edad, sexo, raza, grupo étnico).
- Se le harán preguntas sobre sus antecedentes médicos y sus condiciones clínicas actuales.
- Se le harán preguntas sobre cualquier medicamento que haya estado usando en el pasado y cualquier medicamento que use actualmente. Se le indicará qué medicamentos podrá usar mientras esté en el estudio.
- Se le preguntará cómo se siente.
- Se le harán preguntas acerca de sus antecedentes de tabaquismo.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o antes (para ello, responderá el cuestionario de Prochaska "Etapas de cambio" [*Stage of Change*]).
- Se le preguntará si está preparado para cumplir con los procedimientos descritos en el protocolo del estudio (por ejemplo, si está preparado para abstenerse de fumar durante un máximo de 91 días).
- Se le preguntará qué marca de cigarrillos mentolados normales fuma.
- Se le realizará una exploración física, se medirán los signos vitales (pulso, presión arterial y frecuencia respiratoria estando previamente en posición de decúbito supino durante al menos 5 minutos) y se medirá la estatura y el peso para calcular el índice de masa corporal (IMC).
- Se le realizará un ECG (electrocardiograma, un trazado indoloro del ritmo cardíaco). Un ECG muestra el patrón de los latidos del corazón. Es posible que a los varones se les deba afeitar el vello del pecho antes de los ECG para que los parches se adhieran a la piel. Las mujeres no podrán usar sostén.

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- Se obtendrán muestras de sangre y de orina para realizar análisis de laboratorio clínico, después de un período de ayuno de 10 horas.
- A las mujeres también se les realizará una prueba de embarazo en orina.
- Se realizarán pruebas para la detección de VIH (SIDA) y hepatitis (de una muestra de sangre), drogas ilegales (de una muestra de orina), cotinina (de una muestra de orina) y alcohol (de una muestra de sangre o de una prueba respiratoria).
- Durante esta visita, el personal del estudio llevará a cabo una demostración del producto THS 2.2 Menthol.
- Se realizará una radiografía del pecho si no se ha realizado una dentro de los 6 meses anteriores. La radiografía se llevará a cabo en una unidad de radiología (rayos X). La radiografía del pecho consta de dos imágenes radiográficas que se toman en ángulos diferentes.
- Se le pedirá que sople dentro de una máquina llamada espirómetro. Esto se realizará antes y después de inhalar un broncodilatador de acción rápida (medicamento para “abrir” los bronquios). Esta máquina medirá qué tan bien funcionan los pulmones. Esta prueba se realizará al menos una hora después de fumar.
- Se le pedirá que complete un cuestionario específico sobre la dependencia de la nicotina (Prueba de Fagerstrom de dependencia de nicotina [*Fagerstrom Test for Nicotine Dependence*]).
- Se le entregarán dos formularios de consentimiento informado adicionales para subestudios opcionales. Su participación en el estudio principal no depende de su decisión de firmar o no estos formularios de consentimiento informado.

El virus de inmunodeficiencia humana (VIH) es el virus que puede causar el síndrome de inmunodeficiencia adquirida (SIDA). Para poder reunir los requisitos para participar en este estudio, primero debe obtener un resultado negativo en la prueba de anticuerpos contra el VIH. Los anticuerpos son sustancias que produce el sistema inmunitario del cuerpo para combatir infecciones. Un análisis de sangre puede demostrar si usted ha estado expuesto o está infectado con el VIH. La decisión de aceptar realizarse la prueba de VIH es voluntaria y solamente usted puede tomarla. Sin embargo, si elige no realizarse la prueba de VIH, no podrá participar en este estudio. La prueba de anticuerpos contra el VIH se realizará de forma confidencial. Un resultado VIH positivo no significa que usted tenga VIH o SIDA, así como una prueba con resultado negativo no significa que usted no esté infectado porque puede tardar hasta tres meses que la prueba indique la infección. Los resultados positivos de las pruebas de hepatitis y VIH deben informarse a un organismo de salud local. Esta es la obligación legal de los profesionales de la salud en este estado.

Si no reúne los requisitos para participar en el estudio según los resultados de otros procedimientos de selección, o si usted no completa la visita de selección, es posible que estas pruebas de VIH no se realicen.

Se le comunicará que puede continuar fumando su marca preferida de cigarrillos mentolados convencionales.

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Se le permitirá participar en el estudio a discreción del médico del estudio si los resultados de los análisis de laboratorio de la selección del estudio y de otras evaluaciones realizadas tanto en la selección como el día de la admisión (día -2) son satisfactorios. Es posible que sea necesario repetir los procedimientos de selección para que pueda ingresar en este estudio. Se le comunicarán las restricciones del estudio y cuándo debe regresar a la unidad de investigación para comenzar el estudio.

Es posible que sea necesario repetir algunos procedimientos de selección en el ingreso para confirmar la elegibilidad. Estas pruebas pueden mostrar una modificación desde la selección que indique un cambio en su salud o bienestar físico que quizá haga que usted no sea elegible en el momento del ingreso.

Si después de completar los procedimientos de selección usted reúne los requisitos para el estudio, deberá comprar sus propios cigarrillos mentolados convencionales de la marca que prefiera antes de la admisión. El día -2, deberá entregarle al personal del estudio la cantidad de paquetes que considere que podría fumar durante 9 días más 4 paquetes adicionales. El patrocinador no proporcionará los cigarrillos mentolados convencionales. Los paquetes sin usar o usados parcialmente se le devolverán cuando sea dado de alta del centro.

PROCEDIMIENTOS DEL ESTUDIO

Periódicamente durante el estudio, se medirán los signos vitales (presión arterial, pulso) y se realizarán ECG. También se le harán preguntas para saber cómo se siente y si ha usado algún medicamento. Además, las muestras de sangre y/o de orina obtenidas en este estudio pueden usarse para realizar análisis de laboratorio clínico de rutina, análisis del medicamento del estudio, constituyentes del humo seleccionados, biomarcadores, marcadores de riesgo, niveles de nicotina y monóxido de carbono. También se le pedirá que complete varios cuestionarios sobre los cigarrillos, el hábito de fumar, la preferencia de fumar, su percepción de los riesgos asociados con el uso del producto THS 2.2 Menthol y la abstinencia de fumar. Consulte a continuación la lista de evaluaciones que deberá realizar cada día.

En función del diseño del estudio, es posible que sea seleccionado como suplente para este estudio. En este caso, puede seguir los procedimientos de las secciones Admisión y Visita inicial (día -1 y día 0), pero no será asignado a ningún grupo del estudio ni participará en el resto del estudio.

Día -2 (admisión/ingreso)

El día -2 concurrirá al centro de investigación para comenzar su internamiento en el centro de investigación.

Si es elegible:

- Se le realizará una exploración física, y se medirá su peso y cintura. Se calculará el índice de masa corporal.

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- Se obtendrán muestras de orina para realizar análisis de laboratorio (pruebas para detectar el uso de drogas ilegales y una prueba de embarazo en orina para las mujeres).
- Se le preguntará cómo se siente.
- Se le harán preguntas sobre cualquier medicamento que esté usando actualmente y sus condiciones clínicas actuales.
- Recibirá información sobre el riesgo de fumar/asesoramiento para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se le preguntará acerca de sus antecedentes de tabaquismo.
- Se realizará una prueba de alcohol (en una muestra de orina o una prueba respiratoria).
- Se le preguntará si está preparado para cumplir con los procedimientos descritos en el protocolo del estudio (por ejemplo, si está preparado para abstenerse de fumar durante un máximo de 91 días).
- Se realizará una prueba de medición de monóxido de carbono en el aliento (medición de la cantidad de monóxido de carbono en el aliento).
- Se medirán los signos vitales (presión arterial, frecuencia del pulso, frecuencia respiratoria).
- Se identificará la marca de cigarrillo mentolado convencional que fuma actualmente (deberá entregarle al personal del centro su propio suministro de cigarrillos mentolados convencionales para el período de internamiento. Tomarán una fotografía del paquete).
- Antes de la prueba del producto THS 2.2 Menthol, se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o antes (para ello, responderá el cuestionario de Prochaska "Etapa de cambio").
- Realizará una prueba del producto THS 2.2 Menthol (solamente después de que se confirme un resultado negativo en la prueba de embarazo en las mujeres). Como último procedimiento de los criterios de elegibilidad, probará el producto THS 2.2 Menthol (usando como máximo 3 ramas de tabaco mentolado). A continuación, se le preguntará si está listo para usar el producto THS 2.2 Menthol durante el tiempo que dure el estudio, si fue asignado de forma aleatoria al grupo 1.
- Si cumple con todos los criterios de elegibilidad, será inscrito en el estudio.
- Después de confirmar su inscripción en el estudio, se le preguntará a qué producto preferiría ser asignado de forma aleatoria, si pudiera elegir el grupo del estudio (preguntas de preferencia de producto). Sin embargo, tenga en cuenta que, en realidad, el grupo del estudio en el que ingrese se decidirá de forma aleatoria y usted no puede elegirlo. Si prefiere ser asignado de forma aleatoria al grupo SA, se le pedirá nuevamente que responda el cuestionario de Prochaska "Etapa de cambio". Según su respuesta, es posible que sea retirado del estudio.

Continuará fumando sus propios cigarrillos mentolados convencionales hasta las 11:00 p. m.

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Visita inicial, día -1

- Desde las 10:00 a. m. hasta las 2:00 p. m., usted orinará en recipientes desechables que luego le entregará al personal del centro. El personal del centro le proporcionará información detallada sobre el método de obtención de orina. La orina obtenida se usará para analizar biomarcadores de exposición y marcadores de riesgo.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizarán pruebas de determinación de monóxido de carbono en el aliento cuatro veces por día; la primera prueba se llevará a cabo 15 minutos antes de la primera vez que fume y las otras pruebas tendrán lugar entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m.
- Se medirán los signos vitales (presión arterial, frecuencia cardíaca y frecuencia respiratoria).
- Cuestionario de impulsos de fumar (deseo de fumar) (*Questionnaire of Smoking Urges*): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos (*Modified Cigarette Evaluation Questionnaire*): se le pedirá que complete un cuestionario para evaluar el producto THS 2.2 Menthol y los cigarrillos mentolados convencionales.
- Se le pedirá que complete dos cuestionarios para evaluar su conducta actual y anterior con respecto al hábito de fumar (Cuestionario de factores de riesgo conductuales [*Behavioral Risk Factor Questionnaire*] y Cuestionario sobre el hábito de fumar [*Smoking Questionnaire*]) y datos complementarios sobre la conducta relacionada con el hábito de fumar.
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (una medición de los niveles de monóxido de carbono en la sangre), entre las 8:00 y las 9:30 p. m.
- Se deberán juntar todas las colillas de cigarrillos mentolados convencionales que haya fumado para llevar un control.

Visita inicial, día 0

Lo despertarán temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio.

- Comienzo de la obtención de orina de 24 horas del día 0 (cada vez que orine deberá hacerlo en recipientes desechables que luego le entregará al personal del centro). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará una prueba de determinación de monóxido de carbono en el aliento (cuatro veces por día; la primera prueba se llevará a cabo 15 minutos antes de la primera vez que fume y las otras pruebas tendrán lugar entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m.).
- Se obtendrán muestras de sangre para el día 0 de la siguiente manera:

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- Una muestra para hematología, bioquímica clínica y marcadores de riesgo: se obtendrá después de al menos 10 horas de ayuno.
- Una muestra de sangre para el almacenamiento en banco de material biológico a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (si da su consentimiento para esta muestra) (debe realizarse después de al menos 10 horas de ayuno).
- Una muestra para almacenamiento en banco de material biológico para realizar análisis adicionales de investigación transcriptómica (si dio su consentimiento para una muestra para pruebas genéticas) (se debe realizar después de al menos 10 horas de ayuno).
- Una muestra para medir los oxisteroles ("colesterol") en la sangre (se debe realizar después de al menos 10 horas de ayuno).
- Una muestra para medir la carboxihemoglobina (una medida de la concentración de monóxido de carbono en la sangre) (antes de las pruebas para evaluar la función pulmonar completa)
- Una muestra para medir la actividad de la enzima CYP2A6, una entidad biológica involucrada en el metabolismo de la nicotina en la sangre (se debe realizar antes de fumar).
- Una muestra para medir la actividad de la enzima CYP1A2 (que interviene en el metabolismo de la cafeína), entre las 4:00 y las 5:30 p. m., 6 horas después de haber ingerido un comprimido de cafeína.
- Una muestra para medir la carboxihemoglobina (una medición de los niveles de monóxido de carbono en la sangre), entre las 8:00 y las 9:30 p. m.
- Una muestra para medir los niveles de nicotina y cotinina en la sangre, entre las 8:00 y las 9:30 p. m.
- Tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 200 ml de agua (para medir la enzima CYP1A2), entre las 10:00 y las 11:30 a. m.
- Se realizará una prueba de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes de fumar.
- Se obtendrá una muestra de orina para realizar análisis de seguridad.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Se realizará una topografía del fumador (un procedimiento indoloro para evaluar la conducta con respecto al hábito de fumar) solamente si se le proporciona el dispositivo HST SODIM® (un dispositivo que mide la forma individual de fumar de una persona). Tenga en cuenta que si le entregan el dispositivo HST SODIM®, debe usarlo todas las veces que fume el día 0.
- Cuestionario sobre topografía del fumador: si se le entrega el dispositivo HST SODIM® también se le pedirá que complete un cuestionario para evaluar el uso del HST en rituales relacionados con el hábito de fumar entre las 8:00 y las 11:00 p. m.

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- Evaluación de la tos (se le pedirá que complete un cuestionario en el que se evalúa la tos) y la Escala Minnesota de abstinencia de la nicotina (se le pedirá que complete un cuestionario para evaluar los signos y síntomas de la abstinencia). Los cuestionarios se deben completar antes de fumar, pero no más tarde de las 10:00 a. m.
- Se le pedirá que complete un cuestionario para evaluar el producto (Cuestionario modificado de evaluación de cigarrillos) y un cuestionario para evaluar su deseo de fumar (Cuestionario de impulsos de fumar), entre las 8:00 y las 11:00 p. m.
- Obtención de células epiteliales nasales (obteniones de células de la nariz) y de una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalles si firma el formulario de consentimiento informado correspondiente a cada uno.
- Se recogerán todas las colillas de los cigarrillos mentolados convencionales que haya fumado para llevar un control.

Días 1 a 5 del período de exposición

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio

- Antes de las 6:30 a. m. del día 1, se le comunicará a qué grupo del estudio ha sido asignado de forma aleatoria.
- Recibirá asistencia para abstenerse de fumar, si fuese necesario (solamente el grupo de abstinencia de fumar).
- Se realizará la obtención de orina de 24 horas desde la mañana del día 1 hasta la mañana del día 6 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del centro). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- El día 1 finaliza la obtención de orina de 24 horas que había comenzado el día 0. La orina obtenida durante las 24 horas se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo, además se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para almacenarlas a largo plazo en un banco de material biológico y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- La orina obtenida durante las 24 horas de los días 2, 3, 4 y 5 se usará para analizar los biomarcadores de exposición y la creatinina.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrán muestras de sangre para realizar lo siguiente:
 1. Medición de la carboxihemoglobina: días 1 a 4, una muestra de sangre al anochecer, entre las 8:00 y las 9:30 p. m., cada día. Día 5, una muestra de sangre dentro de los 15 minutos anteriores al primer uso del producto del día, entre las 8:00 y las 9:30 a. m., para los sujetos del grupo de abstinencia de fumar, seguida de tres muestras de sangre adicionales entre las 12:00 y la

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1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m., para todos los sujetos.

2. Medición de la nicotina/cotina: días 1 a 4, una muestra de sangre al anochecer, entre las 8:00 y las 9:30 p. m., cada día. El día 5, solamente para los grupos del producto THS 2.2 Menthol y de cigarrillos mentolados convencionales, una muestra de sangre dentro de los 15 minutos anteriores al primer uso del producto de ese día seguida de ocho muestras a intervalos de 2 horas. Para los sujetos asignados de forma aleatoria al grupo de abstinencia de fumar, el día 5 se obtendrá una muestra de sangre por la mañana, entre las 8:00 y las 9:30 a. m.
- Solamente el día 5, se obtendrá una muestra de sangre para medir la actividad de la enzima CYP1A2 (que interviene en el metabolismo de la cafeína): la muestra se obtendrá entre las 4:00 y las 5:30 p. m., 6 horas después de haber tomado un comprimido de cafeína.
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento, cuatro veces al día: la primera prueba se realizará 15 minutos antes del primer cigarrillo o uso del producto, entre las 8:00 y las 9:30 de la mañana, para los sujetos del grupo de abstinencia de fumar; las otras pruebas se llevarán a cabo aproximadamente entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m. y las 8:00 y las 9:30 p. m., para todos los sujetos (días 1 a 5).
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: días 1 a 5).
- Evaluación de la tos (se le pedirá que complete un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (se le pedirá que complete un cuestionario para evaluar los signos y síntomas de la abstinencia) (debe realizarse antes de fumar, no más tarde de las 10:00 p. m., los días 1 a 5).
- Se le pedirá que complete un cuestionario para evaluar el producto (Cuestionario modificado de evaluación de cigarrillos) y un cuestionario para evaluar su deseo de fumar (Cuestionario de impulsos de fumar), entre las 8:00 y las 11:00 p. m. de los días 1 a 5.
- Solamente el día 4, se le pedirá que complete un cuestionario sobre su estado socioeconómico. Se le hará una serie de preguntas relacionadas con su educación, estado ocupacional, cantidad de personas que viven con usted e ingreso anual de su casa. Puede responder todas las preguntas que desee.
- Solamente el día 4, se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales y se le proporcionó el dispositivo HST SODIM®).
- Solamente el día 5, se le pedirá que complete dos cuestionarios para evaluar su conducta actual y anterior con respecto al hábito de fumar (Cuestionario de factores de riesgo conductuales y Cuestionario sobre el hábito de fumar) y datos complementarios con respecto a la conducta relacionada con el hábito de fumar.
- Solamente el día 5, tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 200 ml de agua (para medir la enzima CYP1A2), entre las 10:00 y las 11:30 a. m.

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- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que si se le entrega el dispositivo HST SODIM®, y está en el grupo del producto THS 2.2 Menthol y de cigarrillos mentolados convencionales, debe utilizarlo para todos los usos de producto (días 1 a 4).

Fumar los cigarrillos mentolados convencionales o usar el producto THS 2.2 Menthol está permitido de 6:30 a. m. a 11:00 p. m., pero no durante los procedimientos del estudio. Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas del producto THS 2.2 Menthol y las colillas de los cigarrillos mentolados convencionales (días 1 a 5). En el grupo del producto THS 2.2 Menthol, se le pedirá que recoja todos los restos de tabaco usados en los frascos exclusivos que le entregará el personal.

Día 6 (alta)

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio

- Recibirá asistencia para abstenerse de fumar, si fuese necesario (solamente el grupo 3).
- Se obtendrán muestras de sangre (que incluyen muestras para medir un perfil de nicotina: se extraerán dos muestras de sangre, la primera tendrá lugar 20 horas después de la hora de inicio del primer uso del producto, el día 5, y la segunda será 24 horas después del inicio del primer uso del producto, el día 5. En el caso del grupo de abstinencia de fumar, se extraerá una sola muestra de sangre entre las 8:00 y las 9:30 a. m.).
- El día 6 finaliza la obtención de orina de 24 horas que comenzó el día 5. Esta muestra se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo; además, se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para el almacenamiento en banco de material biológico a largo plazo y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- Se obtendrán muestras de sangre y de orina para realizar análisis de laboratorio (hematología, bioquímica clínica, después de un período de al menos 10 horas de ayuno), un análisis de orina general y una prueba de embarazo en orina para todas las mujeres.
- Se obtendrán muestras de sangre para realizar análisis de marcadores de riesgo (después de al menos 10 horas de ayuno).
- Se obtendrán muestras de sangre para almacenamiento a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.

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- Se obtendrá una muestra de sangre para almacenamiento a largo plazo para realizar análisis adicionales de transcriptómica (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Se obtendrá una muestra de sangre para medir los oxiesteroles (después de un período de al menos 10 horas de ayuno).
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (antes de la prueba para evaluar la función pulmonar completa).
- Se obtendrá una muestra de sangre para medir la actividad de la enzima CYP2A6 (se debe realizar antes de fumar).
- Se realizará una exploración física que incluye la medición del peso y el cálculo del índice de masa corporal.
- Completará un cuestionario de Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia) (se debe realizar antes del uso del producto, pero no más tarde de las 10:00 a. m.).
- Se realizarán pruebas de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes del uso del producto.
- Se realizará una prueba de determinación de monóxido de carbono en el aliento.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria).
- Se realizará un electrocardiograma (un trazado indoloro del ritmo y la frecuencia cardíaca).
- Se le asesorará sobre el riesgo de fumar y sobre la importancia de dejar de fumar, y se le proporcionará información sobre el producto THS 2.2 Menthol.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrán células epiteliales nasales (obteniones de células de la nariz) y una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalle si firma el formulario de consentimiento informado correspondiente a cada uno.
- Será dado de alta del centro.

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas del producto THS 2.2 Menthol y las colillas de los cigarrillos mentolados convencionales. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Antes ser dado de alta del centro, se le entregará un diario electrónico que usará para registrar cualquier uso de las ramas de tabaco del producto THS 2.2 Menthol, los

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cigarrillos convencionales (mentolados y no mentolados), los productos de terapia de sustitución de la nicotina o el uso de otros productos que contengan nicotina/tabaco. Todos los participantes, incluidos los del grupo 3, deben completar este diario todos los días desde el momento del alta el día 6 hasta el momento del alta el día 91. Recibirá capacitación para usar este diario electrónico.

Después del alta el día 6, se le indicará que continúe utilizando el producto/régimen que se le asignó en su casa durante 86 días. Si se lo asignó al grupo SA, es posible que se le proporcione terapia de sustitución de la nicotina (no se permitirá el uso de ningún otro producto medicinal para dejar de fumar) si el investigador lo considera necesario o si usted lo solicita.

Visita del día 30 (desde el ingreso antes de las 8:30 a. m. del día 30 hasta la salida el día 31) y visita del día 60 (desde el ingreso antes de las 8:30 a. m. hasta la salida el día 61)

Se permitirá fumar o usar el producto en el centro desde el ingreso hasta aproximadamente las 11:00 p. m. de los días 30 y 60 y desde las 6:30 a. m. de los días 31 y 61. No hay restricciones con respecto a fumar/al uso del producto antes del ingreso al centro. Si fue asignado al grupo de cigarrillos mentolados convencionales o al de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol. Durante las visitas de los días 30 y 60, se le pedirá que continúe completando el diario electrónico todos los días.

Se le pedirá que traiga suficiente suministro del producto que ha estado usando para cubrir su estadía durante el internamiento. Se le proporcionarán ramas de tabaco del producto THS 2.2 Menthol durante su estadía en la clínica. Si se lo asigna al grupo del producto THS 2.2, tendrá que traer todos los paquetes vacíos y las ramas de tabaco de producto THS 2.2 sin usar. También deberá traer el dispositivo THS 2.2 (con todas las piezas: las boquillas, el cargador, la herramienta de limpieza, la fuente de energía principal y el cable USB) y el diario electrónico.

Durante los días 30 y 60, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará la obtención de orina de 24 horas desde la mañana de los días 30 y 60 hasta la mañana de los días 31 y 61 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del estudio). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Prueba de embarazo (para las mujeres).
- Obtención de una muestra de sangre para medir la carboxihemoglobina.
- Obtención de una muestra de sangre para medir la nicotina y la cotinina en la

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sangre.

- Exploración física que incluye la medición del peso y el cálculo del índice de masa corporal.
- Se le realizará un ECG (electrocardiograma, un trazado indoloro del ritmo cardíaco).
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Cuestionario de impulsos de fumar (deseo de fumar): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos: se le pedirá que complete un cuestionario para evaluar el producto.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o menos (respondiendo el cuestionario de Prochaska "Etapa de cambio").
- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que el dispositivo HST SODIM® debe utilizarse para todo los usos de producto de los grupos de THS 2.2 Menthol y cigarrillos mentolados convencionales durante un período de 4 horas cada día y solamente con el producto al cual usted ha sido asignado.
- Se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®).

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Días 31 y 61

Durante estos días, usted puede comenzar a fumar/usar el producto desde las 6:30 a. m.

Durante los días 31 y 61, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo 3).
- Preguntas sobre cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Obtención de muestras de sangre para realizar análisis de laboratorio (hematología, bioquímica clínica) y análisis de marcadores de riesgo después de un período de al menos 10 horas de ayuno.
- Finalización de la obtención de orina de 24 horas desde el día 30 o el día 60. La orina obtenida durante 24 horas se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo.

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- Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia).
- Análisis de orina de seguridad.
- Recibirá asesoramiento sobre el riesgo de fumar/para dejar de fumar e información sobre el producto THS 2.2 Menthol.

Visita del día 90 (desde el ingreso antes de las 8:30 a. m. del día 90 hasta el alta el día 91)

Se le pedirá que traiga suficientes ramas de tabaco, de las que ha estado usando, para su estadía en la clínica. Se reabastecerán las ramas de tabaco del producto THS 2.2 durante su estadía en la clínica.

Si es asignado al grupo del producto THS 2.2, para esta visita tendrá que traer todos los paquetes vacíos y las ramas de tabaco de producto THS 2.2 sin usar. También deberá traer el dispositivo de calentamiento de tabaco (con todas las piezas: las boquillas, el cargador, la herramienta de limpieza, la fuente de energía principal y el cable USB) y el diario electrónico. Dejará todos estos suministros en el centro el día 91, cuando sea dado de alta.

Se permitirá fumar o usar el producto en el centro desde el ingreso hasta aproximadamente las 11:00 p. m. y el día 91 solamente después de que se haya completado el cuestionario de Evaluación de la tos y la Escala Minnesota de abstinencia de la nicotina, y una vez que se haya realizado la medición de la actividad de la enzima CYP2A6 y la espirometría. No hay restricciones para fumar/usar el producto antes del ingreso al centro. Si fue asignado al grupo de cigarrillos mentolados convencionales o al de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol.

Durante la visita del día 90, se le pedirá que continúe completando el diario electrónico todos los días.

Día 90

Durante el día 90, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que el dispositivo HST SODIM® debe usarse para todo los usos

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de producto de los grupos de THS 2.2 Menthol y cigarrillos mentolados convencionales durante un período de 4 horas cada día y solamente con el producto al cual usted ha sido asignado.

- Se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®).
- Se realizará la obtención de orina de 24 horas desde la mañana del día 90 hasta la mañana del día 91 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del estudio). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 200 ml de agua.
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento.
- Obtención de una muestra de sangre para medir la carboxihemoglobina.
- Obtención de una muestra de sangre para medir la nicotina y la cotinina en la sangre.
- Obtención de una muestra de sangre para medir la actividad de la enzima CYP1A2, que se realizará 6 horas después de que haya tomado el comprimido de cafeína.
- Obtención de células epiteliales nasales (obteniones de células de la nariz) y de una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalle si firma el formulario de consentimiento informado correspondiente a cada uno.
- Cuestionario de impulsos de fumar (deseo de fumar): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos: se le pedirá que complete un cuestionario para evaluar el producto.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o menos (respondiendo el cuestionario de Prochaska "Etapa de cambio").
- Se le pedirá que complete un cuestionario específico sobre la dependencia de la nicotina (Prueba de Fagerstrom de dependencia de nicotina).

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Día 91

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio.

Durante este día, se realizarán los siguientes procedimientos:

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- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrá una muestra de sangre para medir la actividad de la enzima CYP2A6 en la sangre. Esta muestra de sangre se obtendrá antes de que fume o use el producto THS 2.2 Menthol.
- Se realizarán pruebas de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes del uso del producto.
- Obtención de muestras de sangre para realizar análisis de laboratorio (hematología, bioquímica clínica) y marcadores de riesgo, después de un período de al menos 10 horas de ayuno.
- Una muestra de sangre para medir los oxiesteroles, después de un período de al menos 10 horas de ayuno.
- Un análisis de orina general, y una prueba de embarazo en orina para todas las mujeres.
- Exploración física que incluye la medición del peso, el perímetro de la cintura y el cálculo del índice de masa corporal.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Se le realizará un electrocardiograma, un trazado indoloro del ritmo cardíaco.
- Obtención de muestras de sangre para el almacenamiento a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Obtención de una muestra de sangre para almacenamiento a largo plazo para realizar análisis adicionales de transcriptómica (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Finalización de la obtención de orina de 24 horas que comenzó el día 90. Esta muestra se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo; además, se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para el almacenamiento en banco de material biológico a largo plazo y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- Comienzo de la obtención de orina de 4 horas el día 91 (a partir de las 10:00 a. m. y durante un período de 4 horas, cada vez que orine, lo hará en recipientes desechables que luego le entregará al personal del centro). La orina obtenida se usará para analizar los biomarcadores de exposición y los marcadores de riesgo.

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- Recibirá asesoramiento sobre el riesgo de fumar/para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se le pedirá que complete una Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia).
- Antes de abandonar el centro deberá entregarle al personal del centro el dispositivo THS 2.2 Menthol, las ramas de tabaco del producto THS 2.2 sin usar (si está en el grupo 1) y el diario electrónico.

Período de seguimiento de seguridad:

Habrá un período de seguimiento de seguridad durante 28 días después de la última visita del estudio planificada (alta del día 91 o finalización anticipada). Si se retira del estudio de forma anticipada, ingresará en el período de seguimiento el día que se retire.

Si participó en la prueba del producto del día -2, pero no fue inscrito en el estudio, aun así ingresará en el período de seguimiento de 28 días.

Durante este período de seguimiento de seguridad, debe comunicarle al centro cualquier problema médico nuevo que experimente. El personal del centro también se comunicará con usted para realizar un seguimiento de cualquier problema médico que usted comunique durante el estudio o durante el período de seguimiento que no se haya resuelto después de haber sido dado de alta del centro.

Procedimientos de retirada

Si usted se retira de forma anticipada del estudio por cualquier motivo, es posible que se le pida que complete los análisis de laboratorio y los procedimientos descritos anteriormente en la sección Día 6.

No se le permitirá traer su propia comida o bebida al centro de investigación. Las comidas se servirán según los cronogramas predeterminados para este estudio. Si tiene cualquier pregunta relacionada con las comidas, hable con su médico del estudio. Habrá disponible bocadillos ligeros, frutas y verduras crudas sin restricciones en cualquier momento durante el período de internamiento. El consumo de agua también está permitido sin restricciones. Se les proporcionará a los participantes de todos los grupos del estudio un menú estándar y un cronograma de comidas.

Muestras de sangre y orina

Durante todo el estudio, se extraerán aproximadamente 316 ml de sangre (alrededor de 1 taza y $\frac{1}{4}$). A modo de comparación, una donación estándar de sangre en un centro de obtención de sangre, una vez dentro de cualquier período de 56 días, representa aproximadamente 500 ml (alrededor de 2 tazas) de sangre.

El personal capacitado y cualificado del centro será responsable de la obtención de las muestras de sangre. El volumen total máximo de sangre extraída incluye 40 ml para los

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análisis de seguridad y repetidos, 30 ml para almacenamiento a largo plazo de muestras en un banco de material biológico para realizar análisis adicionales de biomarcadores de exposición en el cuerpo y marcadores de riesgo (solamente si se otorgan los consentimientos adicionales) y 15 ml para el almacenamiento a largo plazo de las muestras en un banco de material biológico para realizar análisis adicionales de transcriptómica (solamente si se otorgan los consentimientos adicionales).

Es posible que se requieran muestras de sangre adicionales si alguno de sus valores de laboratorio fuera anormal. Es posible que sea necesario hacer más de un intento para obtener una muestra de sangre. Pueden obtenerse muestras de sangre adicionales durante el estudio si el médico del estudio lo considera necesario para supervisar su salud. Las muestras de sangre obtenidas se analizarán mediante el uso de métodos validados, a excepción de los oxiesteroles que serán analizados en un laboratorio correctamente equipado. El laboratorio de análisis designado será responsable de conservar las muestras durante este período y de su posterior destrucción. En todo momento durante el estudio, se mantendrá la seguridad de su información personal y su identidad permanecerá anónima.

Las muestras de sangre y de orina para los análisis de laboratorio de seguridad se evaluarán en el centro o en un laboratorio designado, y se conservarán durante aproximadamente 2 meses y luego serán destruidas.

Todas las muestras de sangre y de orina para la medición de biomarcadores de exposición y marcadores de riesgo se analizarán y se conservarán según la documentación relevante del laboratorio.

Las muestras que proporcione solamente se usarán para los objetivos relacionados con el estudio, y no se realizará ningún otro análisis que no sean los análisis relacionados con el estudio que se han descrito en esta hoja de información sin la aprobación suya y del comité de ética.

Todos los datos reunidos se almacenarán durante el tiempo que sea necesario según las leyes, regulaciones y normas vigentes, para garantizar que los datos estén disponibles para las inspecciones del estudio que realicen las autoridades normativas, así como para garantizar la integridad del estudio.

Si bien las investigaciones futuras en las que se usen sus muestras pueden derivar en el desarrollo de nuevos productos, usted no recibirá ninguna compensación por estos productos nuevos. Al aceptar este uso, usted renuncia a todo reclamo de dinero que los investigadores obtengan del uso comercial o de otro tipo de estas muestras.

Responsabilidades del participante de la investigación

Como participante de una investigación, se le pedirá que complete los procedimientos de este estudio, que acuda a la clínica del estudio para hacer todas las visitas programadas, que siga las instrucciones señaladas en este formulario de consentimiento informado y que notifique al médico del estudio si cambia algún dato relacionado con su salud o su disponibilidad para participar en este estudio.

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**Restricciones generales**

- Para evitar la contaminación cruzada de distintos productos, el grupo 1 (THS 2.2 Menthol) y el grupo 2 (cigarrillos mentolados convencionales) deben usar los productos a los que han sido asignado en cabinas para fumar separadas. El grupo 3 (abstinencia de fumar) no podrá estar en la zona de fumadores.
- No debe haber usado medicamentos recetados NI medicamentos de venta libre durante 4 semanas antes del inicio del estudio ni durante todo el estudio, incluido el período de seguimiento de seguridad. Comuníquelo al médico del estudio cualquier medicamento (recetado, de venta libre, suplementos a base de hierbas/vitaminas) que esté tomando. Él podrá decirle si está permitido o no que los tome durante el estudio.
- No debe haber participado en un estudio de investigación dentro de los últimos 3 meses.
- No debe haber donado sangre o plasma (por ejemplo, plasmaféresis) dentro de los 3 meses anteriores a la admisión.

Si es asignado al grupo 1, no podrá fumar ningún cigarrillo mentolado convencional ni usar ningún producto que contenga tabaco/nicotina (incluida la terapia de reemplazo de la nicotina) desde el día 1 (6:30 a. m.) hasta el momento del alta el día 6.

Restricciones alimenticias

- Se servirán comidas y bocadillos estandarizados (y controlados en calorías) a intervalos regulares durante su internamiento en la clínica, excepto cuando se requiera ayuno o se indique lo contrario.
- Durante el período de internamiento, no se permitirá el consumo de carne asada o frita, carnes precocidas ahumadas (por ejemplo, atún, jamón, carne de vaca en conserva y carnes), tocino ahumado y salchichas.
- Durante el período de internamiento, no se permitirá el consumo de alcohol, brócoli, coles de Bruselas, coliflor, jugo de pomelo o toronja, y alimentos y bebidas que contengan xantina (café, té, chocolate, cacao, mate, guaraná, etc.).
- No está permitido el consumo de bebidas que contengan quinina (por ejemplo, agua tónica) durante el período de internamiento.
- Un día antes de la visita del día 90, no debe consumir jugo de pomelo o toronja ni productos que contengan pomelo o toronja, ni bebidas que contengan quinina (por ejemplo, agua tónica). No se permite el consumo de bebidas alcohólicas, coles de Bruselas, coliflor, carne asada, alimentos o bebidas que contengan xantinas (por ejemplo, café, té, chocolate, cacao, mate, guaraná) en el centro durante la visita ambulatoria.
- No se le permitirá traer su propia comida o bebida al centro de investigación.
- Las comidas se servirán según los cronogramas predeterminados para este estudio. Si tiene cualquier pregunta relacionada con las comidas, hable con su médico del estudio.



- Habrá disponible bocadillos ligeros, frutas y verduras crudas sin restricciones en cualquier momento durante el período de internamiento.
- El consumo de agua también está permitido sin restricciones.
- Se les proporcionará a los participantes de todos los grupos del estudio un menú estándar y un cronograma de comidas.

RIESGOS Y MOLESTIAS

Es posible que haya riesgos para usted si participa en este estudio. Como consumidor de tabaco, los riesgos asociados con el uso del tipo de producto con tabaco que consume normalmente seguirán siendo los mismos. En este momento, el uso del producto THS 2.2 Menthol no proporciona ningún riesgo menor de desarrollar enfermedades relacionadas con el tabaco que los cigarrillos de la marca que fuma habitualmente.

Fumar provoca adicción y causa a los fumadores graves enfermedades mortales como cáncer de pulmón, enfermedades pulmonares y cardiovasculares (enfermedad cardíaca), además de otras enfermedades graves. Ningún cigarrillo es seguro. Lo único que se ha demostrado que reduce el riesgo de desarrollar enfermedades relacionadas con fumar en fumadores es dejar de fumar. A pesar de los riesgos atribuibles al tabaquismo, algunos fumadores tienen dificultades para dejar de fumar o deciden seguir fumando.

Fumar tabaco es perjudicial, y los estudios médicos han demostrado que fumar tabaco es una de las causas principales de muchas enfermedades. Si acepta, durante las visitas le proporcionaremos más información sobre los riesgos relacionados con fumar y le asesoraremos para dejar de fumar.

También puede experimentar síntomas de abstinencia y antojos durante todo el estudio, según el grupo al que fue asignado. Es posible que durante este período experimente algunos síntomas conocidos de abstinencia de la nicotina, entre ellos: antojos de tabaco, irritación, ira, problemas de concentración, dolores de cabeza, fatiga, estreñimiento, inquietud, insomnio, mareos y ansiedad.

El uso particular del producto THS 2.2 Menthol puede implicar riesgos para el sujeto (o el embrión o feto, si la participante está embarazada o puede quedar embarazada). Actualmente, estos riesgos son imprevisibles.

Si tiene seguro médico privado, puede que tenga que hacerle saber a los aseguradores que usted tiene intenciones de participar en un proyecto de investigación para que puedan comunicarle si esto afectará su seguro.

Existe la posibilidad de que las distintas pruebas que se llevan a cabo durante el estudio permitan descubrir un problema médico del cual usted no tenía conocimiento previo. Si esto sucede, el médico de la investigación hará los arreglos necesarios para que reciba un tratamiento adecuado y/o, con su permiso, lo derivará a su médico de

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atención primaria.

No se le permitirá usar terapia de sustitución de la nicotina ni otros productos de ayuda para dejar de fumar durante su estadía en la clínica.

Tenga en cuenta que todos los médicos que trabajan en el centro de investigación están capacitados y cuentan con certificación en procedimientos de soporte vital avanzado para tratar cualquier emergencia médica. Los enfermeros y otro personal de la clínica también están capacitados en procedimientos de emergencia.

En estudios clínicos anteriores, se han evaluado versiones anteriores del producto THS 2.2 Menthol, que no han demostrado preocupaciones con respecto a la seguridad. Sin embargo, al participar en este estudio, es posible que usted experimente algunos eventos (incluidos, entre otros, dolor de cabeza, dolor causado por la extracción de sangre y mareos). Si sufre alguno de estos efectos secundarios o cualquier otro efecto secundario, debe buscar ayuda médica y comunicarse con el médico o el personal del estudio.

Es posible que haya otros riesgos para usted mientras participa en este estudio. Puede experimentar algunas molestias asociadas con el uso del producto THS 2.2 Menthol que no se han comunicado con anterioridad. Es posible que haya algunos riesgos desconocidos o poco frecuentes e imprevisibles asociados con el uso de este producto del estudio, incluso reacción alérgica o interacción con fármacos y medicamentos que esté usando. Además, pueden presentarse otros efectos secundarios graves desconocidos, incluso la muerte.

Todas estas ocurrencias se registrarán, y los investigadores y enfermeros le explicarán determinadas medidas para limitarlas. Durante el desarrollo del estudio, un equipo de investigadores y enfermeros capacitados supervisará su salud y su seguridad.

Si experimenta alguno de los efectos secundarios mencionados más arriba u otros síntomas, debe comunicárselo al médico o al personal del estudio de inmediato. Si no le proporciona al médico o al personal del estudio esta información relacionada con cualquier efecto secundario, al participar en este estudio podría ocasionarse involuntariamente un daño.

Si tiene preguntas sobre los signos o síntomas de los efectos secundarios que leyó en este formulario de consentimiento, hágaselas al médico del estudio. Para reducir la posibilidad de lesiones, siempre use el dispositivo de acuerdo con las instrucciones del fabricante. Las advertencias y las instrucciones de seguridad incluidas en el Manual del usuario no cubren todos los posibles problemas médicos y las situaciones que podrían ocurrir. Consulte el Manual del usuario para obtener más información.

RIESGOS DE LOS PROCEDIMIENTOS DEL ESTUDIO

Durante la obtención de las muestras de sangre, es posible que experimente dolor y/o la

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formación de moretones en el sitio en que se inserta la aguja/el catéter o el lugar donde se coloca el brazalete para medir la presión arterial. Aunque es raro, puede haber formación localizada de coágulos, daños en los nervios e infecciones. También puede experimentar sensación de desvanecimiento y/o desmayos durante la extracción de sangre o poco después.

Los electrodos del ECG pueden causar una reacción en la piel, como enrojecimiento o picazón. Usted también puede presentar molestias en la piel y/o pérdida de vello localizadas asociadas con la colocación de los electrodos del ECG.

Radiografías: si es necesario realizar una radiografía del pecho durante el proceso de selección para este estudio, la exposición a la radiación de una radiografía equivale a aproximadamente 3 días de exposición a la radiación ambiental natural.

Espirometría: para este procedimiento se usará un broncodilatador de acción rápida (medicamento para abrir los bronquios). Es posible que haya un riesgo pequeño de una reacción adversa a este medicamento (como la sensación de que el corazón late más rápido [palpitaciones] o temblores/sacudidas leves). Debe comunicarle al médico del estudio de inmediato cualquier síntoma que pueda experimentar mientras usa este medicamento. Los procedimientos se llevarán a cabo según las normas internacional y científicamente aceptadas.

RIESGOS DESCONOCIDOS/IMPREVISIBLES

Además de los riesgos mencionados anteriormente, pueden existir algunos riesgos desconocidos, poco frecuentes e imprevisibles asociados al uso de estos productos, que incluyen reacciones alérgicas graves o que ponen en riesgo la vida, o interacciones inesperadas con otro medicamento. Se le comunicará oportunamente, tanto en forma oral como escrita, toda nueva información, hallazgo o cambio en la forma en que se llevará a cabo la investigación que pudiera influir sobre su deseo de seguir participando en este estudio.

Si sufre una lesión, un efecto malo o cualquier otra experiencia de salud inusual durante este estudio, debe comunicarse con el médico o el personal del estudio de inmediato.

RIESGOS PARA UN BEBÉ EN GESTACIÓN

Riesgos en el embarazo/para el feto: se sabe que los efectos de fumar para un niño en gestación son dañinos. No debe estar embarazada para participar en este estudio. Es importante que use los siguientes métodos anticonceptivos adecuados durante todo el estudio y hasta la finalización del periodo de seguimiento de seguridad, y que las mujeres no queden embarazadas ni amamenten a un bebé.

- Dispositivo o sistema intrauterino (DIU).
- Uso establecido de métodos hormonales orales/inyectables/implantables/transdérmicos.
- Métodos anticonceptivos de barrera.

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- Preservativos ○ capuchones oclusivos (diafragma) con espuma/gel/película/supositorio espermicida.
- Pareja(s) que se haya(n) realizado una vasectomía.
- Abstinencia verdadera (la abstinencia periódica y el coito interrumpido no son métodos eficaces).

No es necesario usar anticonceptivos, si se ha practicado histerectomía, ligadura de trompas, ovariectomía bilateral o si es posmenopáusica. El estado posmenopáusico se define como mujeres que no han tenido ciclos menstruales durante más de 12 meses. Se debe realizar una prueba de la hormona foliculoestimulante, cuyo resultado debe estar dentro de los límites aceptables.

Si cree que ha quedado embarazada durante el estudio, es importante que se lo comunique al médico del estudio de inmediato. Si queda embarazada o cree que puede estar embarazada, será retirada del estudio y el médico del estudio la derivará para que reciba atención obstétrica. El costo de esa atención será responsabilidad suya. Es posible que el médico del estudio le pida hacer un seguimiento de su embarazo, y le informará al patrocinador y al Comité de Revisión Independiente (*Independent Review Board*, IRB) sobre el embarazo y su desenlace.

BENEFICIOS

La participación en este estudio tiene fines exclusivamente de investigación y no mejorará su salud ni tratará cualquier problema médico que pueda tener. Puede beneficiarse por la realización de las exploraciones físicas. Los resultados de los análisis de laboratorio realizados durante la visita de selección se pondrán a su disposición si lo solicita. Sin embargo, si usted no reúne los requisitos para participar en el estudio según otros procedimientos de selección, es posible que no se realicen algunos análisis de laboratorio.

Este estudio se realiza únicamente con fines de investigación. No hay ningún beneficio directo para usted por participar en el estudio, excepto que recibirá un examen de la salud y asesoramiento para dejar de fumar. Los resultados del estudio ayudarán al patrocinador a comprender mejor la seguridad del producto THS 2.2 Menthol y qué tan bien el cuerpo absorbe la nicotina que contiene el producto. Esta información puede ayudar a otras personas en el futuro.

ALTERNATIVAS AL TRATAMIENTO

En este estudio, no se administra ningún medicamento en estudio. Por lo tanto, no hay ningún tratamiento alternativo que corresponda como parte de este estudio. Sin embargo, si decide que desea dejar de fumar, el personal del estudio le proporcionará información sobre cómo buscar ayuda para hacerlo.

COSTO

Participar en este estudio de investigación no implica ningún costo. El producto THS 2.2 Menthol, los procedimientos relacionados con el estudio y las visitas del estudio se proporcionarán sin cargo para usted ni para su compañía de seguros.

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**COMPENSACIÓN POR PARTICIPAR EN ESTE ESTUDIO**

Será compensado por participar en este estudio de investigación según lo detallado a continuación. Esta compensación es por su tiempo y los inconvenientes causados. Recibirá una compensación según el siguiente programa.

Programa de compensación

Visita de selección	-0-
Visita de selección para realizar una radiografía del pecho	\$50.00
Noches de internamiento en el centro de investigación (11 noches x \$250.00)	\$2750.00
Visita extendida como paciente ambulatorio (3 visitas x \$200)	\$600.00
Diarios (por semana), 14 semanas x \$100	\$1400.00
Finalización del estudio	\$720.00
TOTAL	\$5520.00

La compensación total del estudio completo será de \$5520. Si elige retirarse del estudio de investigación, recibirá una compensación solamente por la parte del estudio que haya completado según lo detallado más arriba. Si Covance debe comprarle cigarrillos mentolados convencionales porque se le acabaron durante el período de confinamiento, la cantidad que se haya gastado se deducirá del total de su compensación.

Si se retira del estudio de forma anticipada debido a un evento médico importante o si el patrocinador cancela el estudio, recibirá una compensación de un importe correspondiente a la parte de la compensación del estudio completo en función de la cantidad de visitas que haya realizado.

Si es seleccionado como un suplente y no es seleccionado para participar en el estudio, recibirá una compensación de \$250.00 para cada noche. Si como suplente obtiene un resultado positivo en las pruebas de detección de cualquier droga no autorizada o de alcohol, no recibirá ninguna compensación.

Todos los participantes de la investigación recibirán su compensación dentro de los 21 días posteriores a la finalización de su participación en el estudio.

Si participa en este estudio, acepta que no será considerado un empleado de Covance o de Philip Morris Products S.A.

No se deducen impuestos de su cheque. Usted es responsable del pago de cualquier impuesto estatal, federal o de seguro social. Deberá proporcionarle a Covance su número de seguro social o número de identificación fiscal, si lo tiene. Si recibe de

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Covance más de \$600 en un año calendario, se le entregará el formulario de impuestos 1099 en el siguiente mes de enero. Covance comunica el dinero que usted recibe al Servicio de Impuestos Internos (*Internal Revenue Service*, IRS).

Si no tiene un número de seguro social o un número de identificación fiscal, el Servicio de Impuestos Internos (IRS) le exige a Covance deducir el 30% de su compensación. Deberá seguir la normativa del IRS para determinar si es elegible para recibir un reembolso, o bien, comunicarse con un contador especializado en impuestos para que le ayude.

DERECHO A RETIRARSE O SER RETIRADO DEL ESTUDIO

Su participación en este estudio es voluntaria. Usted es libre de retirarse de este estudio en cualquier momento; sin embargo, debe comunicarle inmediatamente al médico del estudio si tiene previsto retirarse. Su decisión de participar en este estudio o de retirarse de él no influirá sobre la disponibilidad de su atención médica futura y no implicará sanciones ni pérdida de los beneficios a los que tenga derecho. Puede retirarse de este estudio en cualquier momento. Puede retirar su consentimiento para usar y divulgar su información en cualquier momento. Si usted retira su consentimiento, no podrá seguir participando en este estudio. Si por cualquier motivo se retira o abandona el estudio de forma anticipada, se le pedirá que complete los procedimientos del alta del día 6.

El patrocinador del estudio o el médico a cargo del estudio pueden retirarlo de este estudio sin su consentimiento por cualquier motivo, entre otros:

- El patrocinador o el médico del estudio consideran que un problema médico o una circunstancia puede poner en peligro su bienestar o la integridad del estudio.
- Si usted no sigue las instrucciones del equipo del estudio.
- Si el patrocinador y/o los médicos que participan en el estudio detienen el estudio antes de su finalización o el patrocinador pide que se lo retire del estudio.

CONFIDENCIALIDAD

Si acepta participar en el estudio de investigación, el personal del estudio reunirá, registrará y almacenará información sobre su identidad, salud y participación.

El patrocinador y sus representantes, la Administración de Alimentos y Medicamentos (FDA) de los Estados Unidos, otras autoridades de salud y el Comité de Revisión Independiente MidLands pueden inspeccionar sus registros médicos en papel o en forma electrónica que posiblemente incluyan su nombre, dirección y otra información personal que permita identificarlo. Si fuera necesario, se pueden copiar todos sus registros médicos o parte de ellos durante estas inspecciones.



Los resultados de este estudio de investigación pueden presentarse en conferencias o pueden incluirse en publicaciones. Sin embargo, usted no será identificado personalmente en ninguna presentación o publicación.

Debido a la necesidad de usar información según lo observado más arriba, no se puede garantizar la confidencialidad absoluta.

Habrà una descripción de este ensayo clínico disponible en www.ClinicalTrials.gov, según lo exigen las leyes de los Estados Unidos. Este sitio web no incluirá información que pueda identificarlo. A lo sumo, incluirá un resumen de los resultados. Puede consultar este sitio web en cualquier momento.

CONFIDENCIALIDAD COMERCIAL

La información y todo material o artículo que se le entregue relacionado con el estudio o durante el estudio, como información que permite identificar la unidad de investigación, el patrocinador, cualquier producto del estudio y/o el tipo de estudio que se está realizando, se deberá considerar información comercial confidencial de Covance y el patrocinador del estudio. Por supuesto que usted es libre de analizar esta información confidencial con otras personas, como su médico o sus amigos y familiares, para considerar la posibilidad de participar o no en este estudio o en cualquier momento en que analice su atención médica presente o futura, o sus derechos. Sin embargo, se prohíbe la distribución de información comercial confidencial según lo descrito más arriba en cualquier medio de comunicación o su publicación en Internet.

¿QUIÉN ORGANIZA ESTA INVESTIGACIÓN?

La empresa que patrocina este estudio es Philip Morris Products S.A., Suiza (incluidos los agentes, contratistas o consultores).

¿QUIÉN HA REVISADO EL ESTUDIO?

El Comité de Revisión Independiente MidLands (MLIRB) ha revisado los objetivos y la realización propuesta del estudio principal.

EN CASO DE LESIONES

Su seguridad es la principal preocupación de cada miembro del personal. Comuníquese con el personal del estudio lo antes posible si tiene efectos secundarios o lesiones. El número de teléfono de Covance Dallas Clinical Research Unit es 214-920-9053.

Covance le proporcionará tratamiento médico inmediato, sin costo para usted, por los efectos secundarios o las lesiones que hayan sido causadas por participar en este estudio. Los gastos médicos en los que incurra por cualquier lesión relacionada con la investigación, diferentes de los costos del tratamiento médico inmediato, serán responsabilidad suya o de un tercero pagador. No se le impide que busque obtener compensación por una lesión relacionada con negligencia, fallas, o culpa de las personas involucradas en la investigación.

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Al firmar este formulario de consentimiento, usted **NO RENUNCIA** a ninguno de sus derechos legales.

CONTACTO DE EMERGENCIA

Si durante el estudio experimenta cualquier problema médico o sufre una lesión relacionada con la investigación, comuníquese con el médico del estudio llamando al número de teléfono que figura en la página uno de este documento de consentimiento. Si busca atención de emergencia o requiere internamiento, comuníquelo al médico que lo trate que usted está participando en un estudio de investigación dirigido por el médico del estudio que se menciona en la página uno de este documento.

PERSONAS QUE DEBEN CONTACTARSE PARA PREGUNTAS, PREOCUPACIONES O QUEJAS

Si tiene alguna pregunta o algún problema, si cree que puede haber sufrido una lesión relacionada con la investigación, o si tiene preguntas sobre la disponibilidad de atención médica, debe comunicarse con el Dr. William Lewis llamando al 214-920-9053.

Si tiene preguntas sobre sus derechos, preguntas generales, quejas o preocupaciones sobre esta investigación, o preguntas sobre sus derechos como una persona que participa en este estudio, llame al Comité de Revisión Independiente MidLands (MLIRB) al (913) 385-1414 o al (800) 636-4445. Si en cualquier momento durante o después de su participación en esta investigación, le gustaría recibir información u ofrecer datos sobre su experiencia en la investigación, puede llamar al IRB MidLands al número que figura más arriba o puede visitar el sitio web del IRB MidLands en www.mlirb.com y enviarnos sus comentarios. En cualquier caso, no tiene que darnos su nombre, si no lo desea.

Usted tiene derecho a hacer cualquier pregunta sobre los peligros potenciales y/o conocidos de este estudio en cualquier momento. Si tiene cualquier pregunta sobre su participación en este estudio, o si en cualquier momento cree haber experimentado una lesión relacionada con la investigación o una reacción al medicamento del estudio, comuníquese con el Dr. William Lewis llamando al 214-920-9053.

DERECHOS LEGALES

Al firmar este formulario de consentimiento, usted no perderá ninguno de sus derechos legales a los que tenga derecho de otro modo.

DECLARACIÓN DE CIERRE

Usted ha leído cuidadosamente la información anterior. Además, ha recibido respuestas satisfactorias a todas las preguntas que ha hecho y firma voluntariamente este formulario de consentimiento. Recibirá una copia del documento de consentimiento informado firmado. Por la presente, acepta voluntariamente participar en este estudio.

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Puede retirar este consentimiento en cualquier momento.

NOTIFICACIÓN AL MÉDICO DE CABECERA

Después de que se hayan realizado todas las pruebas de elegibilidad y se haya determinado que usted es apto para ingresar en el estudio, si lo desea, le comunicaremos a su médico particular que está participando en este estudio de investigación. Marque su preferencia a continuación.

- ☐ Sí, quiero que el médico del estudio le informe a mi médico particular acerca de mi participación en este estudio.

Nombre, dirección y número de teléfono del médico particular

- ☐ No, no quiero que el médico del estudio le informe a mi médico particular acerca de mi participación en este estudio.
- ☐ No tengo un médico particular.

**FIRMAS****Lea el párrafo siguiente en voz alta a la persona que obtiene el consentimiento.**

- He leído la información anterior en un idioma que comprendo bien.
- Me han explicado el contenido y el significado de esta información.
- He tenido la oportunidad de hacer mis preguntas en privado así como reunirme con un médico del estudio para analizar este estudio.
- He hecho al personal las preguntas que pueda haber tenido y he tenido tiempo suficiente para decidir si quiero participar en este estudio.
- Por medio del presente, acepto y me ofrezco voluntariamente a participar en este estudio, y autorizo el uso y la divulgación de información médica sobre mi persona.
- También acepto que se realicen las pruebas de VIH descritas en este documento.
- Dono voluntaria y libremente todas las muestras de sangre y orina para la investigación descrita más arriba, y por el presente, renuncio a todos los derechos de propiedad, título e interés que pueda tener sobre esas muestras.
- Acepto mantener la confidencialidad de toda la información relacionada con el producto del estudio (THS 2.2 Menthol), que incluye el diseño del producto, las especificaciones y el método de funcionamiento.

Nombre del participante en letra de imprenta

Firma del participante

Fecha

Hora

Nombre en letra de imprenta de la
persona que realiza el análisis del
consentimiento informado
y la verificación del alfabetismoFirma de la persona que
realiza el análisis del
consentimiento informado
y la verificación del alfabetismo

Fecha

Hora

He recibido una copia firmada y fechada del formulario de consentimiento de este estudio para que la guarde.**Su firma****Fecha**

Para completar únicamente por el personal de Covance:

QC'd by _____

Date _____

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**AUTORIZACIÓN Y CONSENTIMIENTO PARA USAR Y DIVULGAR
INFORMACIÓN DE SALUD PROTEGIDA PARA INVESTIGACIÓN**

Durante su participación en este estudio de investigación, el médico y el personal del estudio obtendrán o generarán información médica personal sobre usted (por ejemplo, registros médicos y resultados de todas las pruebas, los exámenes o los procedimientos que se realicen mientras participa en el estudio) y la registrarán en documentos del estudio. El médico del estudio conservará esta información médica de salud personal en sus registros relacionados con el estudio (a los que haremos referencia como "sus registros del estudio"). Además, el médico del estudio puede obtener, e incluir en sus registros, información sobre su salud y/o sus problemas físicos o mentales pasados, presentes y/o futuros. Es posible que el médico del estudio le pida que firme otra autorización para obtener parte o todos sus registros médicos de su médico. Sus registros del estudio pueden incluir otra información personal (como el número de seguro social, números de registros médicos, fecha de nacimiento, etc.), que podrían usarse para identificarlo. La información de la salud que podría identificarlo se llama "información de salud protegida" (*protected health information*, PHI).

Cuando corresponda de acuerdo con las leyes federales (la "Norma de privacidad") u otras leyes vigentes, su PHI creada u obtenida durante este estudio de investigación no podrá "usarse" para realizar la investigación ni "divulgarse" (entregarse a ninguna persona o entidad) con fines de investigación sin su permiso o consentimiento. Este permiso y consentimiento se llama "autorización". Por lo tanto, usted no puede participar en este estudio a menos que dé su permiso para usar y divulgar su PHI firmando esta autorización. Al firmar, está aceptando permitir al médico y al personal del estudio el uso de su PHI para llevar a cabo este estudio.

Al firmar esta autorización, usted también está aceptando permitir al médico y al personal del estudio que divulguen su PHI a las personas y los grupos que se describen a continuación:

- El patrocinador de este estudio (PATROCINADOR) y cualquier persona que trabaje en representación del patrocinador para llevar a cabo este estudio (a quienes se hace referencia como "el patrocinador"). El patrocinador analizará y evaluará la PHI, y puede usarla para desarrollar nuevas pruebas, procedimientos y productos comerciales. El personal del estudio le asignará un código numérico y/o letras a sus registros, lo que significa que usted no será habitualmente identificado en los registros que se envíen al patrocinador. Sin embargo, el patrocinador podrá ver sus registros completos del estudio o recibir información relacionada con las muestras que lo identifican. Además, el patrocinador puede visitar el centro del estudio para supervisar la forma en que se está efectuando el estudio, y puede revisar su PHI durante estas visitas, para asegurarse de que la información sea correcta.
- El Comité de Revisión Independiente ("IRB") puede tener acceso a su PHI en relación con sus responsabilidades como Comité de Revisión Institucional.

El médico o el patrocinador del estudio pueden divulgar su PHI a la Administración de

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Alimentos y Medicamentos ("FDA") de los Estados Unidos u organismos reguladores similares en Estados Unidos y/o países extranjeros.

Estas divulgaciones también ayudan a asegurar que la información relacionada con la investigación esté disponible para todas las partes que puedan necesitarla con fines de investigación.

Excepto las divulgaciones descritas anteriormente, su PHI no se compartirá con otras personas o entidades a menos que lo requiera la ley. Si su PHI se entrega a las partes mencionadas anteriormente y/o a otras personas o entidades que no están obligadas a cumplir las leyes vigentes, es posible que su PHI ya no esté protegida por estas leyes y posiblemente se use o divulgue de maneras diferentes a las descritas aquí.

Tiene derecho a ver y a hacer copias de su PHI. Sin embargo, al firmar este documento, usted acepta que no podrá ver ni copiar su PHI, ya sea total o parcialmente, hasta que el patrocinador haya completado todo el trabajo relacionado con este estudio. En ese momento, podrá pedir ver sus registros.

Esta autorización no tiene fecha de vencimiento a partir de la fecha en que la firme, a menos que la revoque (cancele o retire) antes.

Tiene derecho a revocar su autorización en cualquier momento. Si la revoca, su PHI dejará de usarse para este estudio, excepto en la medida en que las partes vinculadas con la investigación ya hubieran actuado teniendo en cuenta su autorización o necesiten la información para completar análisis e informes de esta investigación. Para revocar su autorización, debe escribir al médico del estudio a la dirección que figura en la primera página de este formulario, manifestando que revoca su autorización para el uso y la divulgación de la información de salud protegida. Si revoca esta autorización, no podrá continuar participando en este estudio.

Recibirá una copia de esta autorización fechada y firmada después de que la haya firmado.

Firma del sujeto

Fecha

Nombre del sujeto en letra de imprenta

Firma de la persona que obtiene la autorización

Fecha

Nombre en letra de imprenta de la persona que obtiene la autorización

Para completar únicamente por el personal de Covance:

QC'd by _____

Date _____

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APPROVED BY
JAN 30 2014
MLIRB
Medwatch Independent Review Board

**AUTORIZACIÓN Y CONSENTIMIENTO INFORMADO PARA PARTICIPAR
EN UNA INVESTIGACIÓN CLÍNICA**

Título del estudio. Estudio aleatorizado, controlado, abierto, multicéntrico, de 3 grupos paralelos, para demostrar las reducciones en la exposición a constituyentes del humo seleccionados en fumadores aparentemente sanos que cambian al sistema de calentamiento de tabaco mentolado 2.2 (THS 2.2 Menthol) o dejan de fumar, en comparación con continuar usando cigarrillos mentolados convencionales, durante 5 días en internamiento y 86 días más en un contexto ambulatorio.

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Número de selección del sujeto:	<input type="text"/>
Investigador principal: (médico del estudio)	Covance Dallas Site Dr. William Lewis
Dirección del centro de investigación:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Número de teléfono:	Covance Dallas Site Teléfono: 214-920-9053
Número de teléfono las 24 horas:	Covance Dallas Site Teléfono: 972-955-5373
Patrocinador:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Suiza

Se le invita a participar en un estudio de investigación. Sin embargo, antes de que dé su consentimiento para participar en el estudio, lea lo siguiente y haga todas las preguntas que sean necesarias para asegurarnos de que comprende qué implicará su participación. Se le entregará una copia de este formulario de consentimiento informado para que se la lleve a su casa.

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INTRODUCCIÓN

Su participación en este estudio de investigación es voluntaria. Es importante que lea y comprenda la siguiente explicación de los procedimientos propuestos. Este formulario de consentimiento informado describe el objetivo, los procedimientos, los beneficios, las alternativas, los riesgos conocidos o reconocidos, las molestias y las precauciones del estudio, e incluye la duración y la naturaleza de su participación. También describe su derecho a retirarse del estudio en cualquier momento. Para ingresar en el estudio, debe firmar y fechar este formulario de consentimiento en calidad de participante de la investigación.

Tenga en cuenta lo siguiente: si no es absolutamente sincero con el médico respecto a sus antecedentes de salud, que incluyen alergias y uso de medicamentos, podría perjudicarse al participar en este estudio.

NATURALEZA Y OBJETIVO DEL ESTUDIO

El patrocinador de este estudio es Philip Morris Products, un fabricante de productos que contienen tabaco. El patrocinador está desarrollando un enfoque alternativo a los cigarrillos convencionales (normales) a través de un producto que posiblemente permita reducir algunos riesgos de las enfermedades relacionadas con el tabaco.

El sistema de calentamiento de tabaco mentolado 2.2 (*tobacco heating system*, THS 2.2 Menthol) es un producto en fase de investigación que se está desarrollando como una alternativa en lugar de los cigarrillos convencionales que no ha sido aprobada por la Administración de Alimentos y Medicamentos (*Food and Drug Administration*, FDA) de los Estados Unidos.

Se cree que al calentar el tabaco, en lugar de quemarlo como ocurre con los cigarrillos convencionales, es posible que se reduzcan los efectos perjudiciales de fumar.

No se ha demostrado que el producto THS 2.2 Menthol reduzca las enfermedades relacionadas con el consumo de tabaco y usted no debe suponer que los riesgos asociados al uso del producto THS 2.2 Menthol sean diferentes de los que produce fumar cigarrillos comunes.

El objetivo general de este estudio es reunir información sobre el uso del producto en fase de investigación THS 2.2 Menthol cuando se proporciona a los participantes de una investigación que están hospitalizados en el centro de investigación y luego en un contexto ambulatorio. El estudio de investigación comparará el uso del producto THS 2.2 Menthol con los cigarrillos mentolados convencionales y la abstinencia de fumar. Durante este estudio se medirán varios biomarcadores de exposición presentes en el cuerpo y marcadores de riesgo. El estudio también obtendrá información de seguridad relacionada con el uso del producto THS 2.2 Menthol.

Los biomarcadores de exposición son sustancias que se miden en el cuerpo como el resultado del consumo de otra sustancia (como el humo de cigarrillo). Por ejemplo,

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cuando fuma usted inhala monóxido de carbono. El monóxido de carbono se une a determinada parte de los glóbulos rojos llamada hemoglobina. El monóxido de carbono puede reemplazar al oxígeno presente en los glóbulos rojos. En este estudio, se medirá el nivel de monóxido de carbono unido a la hemoglobina y se hará referencia a este nivel como un biomarcador de exposición al monóxido de carbono.

Un marcador de riesgo es una característica biológica que se asocia a un mayor riesgo de desarrollar determinadas enfermedades o infecciones. Para comprender las diferencias biológicas (fisiológicas) entre el producto THS 2.2 Menthol, los cigarrillos mentolados convencionales y la abstinencia de fumar, se tomarán otras mediciones, incluidos los marcadores de irritación (inflamación) de la nariz y de los tipos de colesterol en la sangre.

Los objetivos adicionales de este estudio de investigación son comprender mejor lo que el cuerpo hace con la nicotina y sus productos de degradación (incluidas las enzimas que intervienen en la degradación) en los fumadores que cambian de cigarrillos mentolados convencionales al producto THS 2.2 Menthol en comparación con los fumadores que continúan fumando cigarrillos mentolados convencionales. Además, en este estudio se evaluarán los patrones y las preferencias del hábito de fumar (es decir, la topografía del fumador), el uso del producto y los efectos subjetivos relacionados.

Este estudio tiene solamente fines de investigación y no está destinado a tratar ningún problema médico.

También se le invitará a participar en dos subestudios adicionales, opcionales. En uno, se realizarán análisis farmacogenómicos de sus muestras biológicas. No está obligado a participar en ninguno de estos dos subestudios opcionales. Se le entregarán 2 formularios de consentimiento informado separados para estos subestudios adicionales. **Si no desea participar en estos subestudios adicionales, su participación en este estudio de investigación principal no se verá afectada.**

Covance Clinical Research Unit Inc. recibe un pago por evaluar el producto en fase de investigación THS 2.2 Menthol. Los médicos de este estudio trabajan para Covance, pero no tienen ningún interés económico en los resultados de este estudio.

¿QUÉ PRODUCTO SE ESTÁ EVALUANDO?

El producto que desarrolla el patrocinador y que se evalúa en este estudio se llama THS 2.2 Menthol. Este producto mantiene el calentamiento del tabaco a una temperatura mucho más baja que la que se observa en los cigarrillos normales (convencionales). El producto THS 2.2 Menthol consta de los siguientes componentes: las ramas de tabaco mentolado para el THS (ramas de tabaco mentolado), la boquilla, el cargador, una herramienta para limpieza, una fuente de energía principal y un cable USB.

El dispositivo de calentamiento de tabaco comprende todos estos componentes en el producto THS 2.2 Menthol, excepto las ramas de tabaco mentolado. La función de la

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boquilla es calentar la rama de tabaco mentolado, lo que produce un aerosol que recibe el usuario. El calentamiento eléctrico funciona con una batería interna que genera energía durante aproximadamente 6 minutos (lo que alcanza para el uso completo de una sola rama de tabaco). A diferencia de los cigarrillos normales, las ramas de tabaco mentolado no se queman durante el consumo y el largo sigue siendo el mismo después de su uso.

En este momento, es importante que usted comprenda que no se ha demostrado que el producto THS 2.2 Menthol reduzca las enfermedades relacionadas con el tabaco y no debe suponer que los riesgos asociados con el uso de este producto sean diferentes de los que se relacionan con fumar cigarrillos normales.

SELECCIÓN DE LOS PARTICIPANTES DE LA INVESTIGACIÓN

Se le invita a participar en este estudio porque usted es una fumadora o un fumador aparentemente sano que tiene más de 22 años de edad y fuma cigarrillos mentolados convencionales, y posiblemente sea apto para participar en este estudio.

Si está pensando seriamente en dejar de fumar en los próximos 6 meses, usted no califica para participar en este estudio. Sin embargo, debe estar dispuesto(a) a abstenerse de fumar durante el estudio si resulta seleccionado al azar para el grupo de abstinencia del tabaco.

Si es una mujer, no debe estar embarazada ni amamantando. Si decide participar en este estudio, se le pedirá que use métodos anticonceptivos adecuados durante el estudio.

Es importante que responda completamente y con sinceridad todas las preguntas de selección. Debe comunicar todas las enfermedades y alergias actuales y anteriores, así como todos los medicamentos que esté usando, incluidos los medicamentos recetados y de venta libre. **Si no revela toda la información sobre sus antecedentes médicos, cualquier problema médico que usted tenga y los medicamentos que ha usado, podría ser peligroso para su salud.**

En este estudio de investigación multicéntrico, se asignarán de forma aleatoria 160 participantes.

DURACIÓN DEL ESTUDIO

La duración de su participación en este estudio es de aproximadamente 123 a 150 días incluido el período de selección. Se realizará una visita de selección como máximo 28 días (día -30 a día -3) antes de la admisión en el centro de investigación (para determinar si usted reúne los requisitos para este estudio de investigación). Este estudio requiere un internamiento de 9 días y 8 noches (día -2 a día 6) en el centro de investigación seguida de 3 visitas los días 30 a 31, 60 a 61 y 90 a 91. Cada visita constará de 2 días consecutivos (con estadía de 1 noche en cada visita) en el centro. En la visita del día 30, ingresará al centro antes de las 8:30 a. m. y saldrá después de que se hayan realizado todas las evaluaciones del día 31. En la visita del día 60, ingresará al centro antes de las 8:30 a. m. del día 60 y saldrá después de que se hayan

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realizado todas las evaluaciones del día 61. En la visita del día 90, ingresará al centro antes de las 8:30 a. m. del día 90 y será dado de alta el día 91, después de que se hayan realizado todas las evaluaciones.

Después del día 91, habrá un período de seguimiento de seguridad de 28 días durante el cual debe comunicarle al personal del centro cualquier problema médico nuevo que tenga. El personal del centro también se comunicará con usted para realizar un seguimiento de cualquier problema médico que usted comunique durante el estudio o durante el período de seguimiento que no se haya resuelto después de haber sido dado de alta del centro, el día 91.

Durante el estudio, desde la selección hasta la finalización del período de seguimiento de seguridad, siempre debe comunicarse con el centro antes de tomar cualquier medicamento (recetado o de venta libre).

DISEÑO DEL ESTUDIO

Este estudio de investigación será de “diseño abierto”. Esto significa que usted, el médico del estudio y el patrocinador sabrán qué productos recibe. Una vez que se determine que usted reúne los requisitos para el estudio, será asignado de forma aleatoria (al azar, como cuando se arroja una moneda al aire) a 1 de los siguientes 3 grupos del estudio. Esto se realizará el día 0. El día 1, se le comunicará el grupo al cual fue asignado. Usted no podrá elegir el grupo al cual es asignado.

Usted tiene un 50% de probabilidades de estar en el grupo 1 y un 25% de estar en el grupo 2 o 3.

- **Grupo 1:** grupo del sistema de calentamiento de tabaco, THS 2.2 Menthol (80 participantes).
- **Grupo 2:** grupo de cigarrillos mentolados convencionales (40 participantes).
- **Grupo 3:** grupo de abstinencia de fumar (40 participantes).

Si es asignado al grupo 1 o 2, se le permitirá fumar durante el período de internamiento (desde el día 1 hasta el momento en que sea dado de alta del centro, el día 6) entre las 6:30 a. m. y las 11:00 p. m. cada día. Durante este período, usted puede usar la cantidad de ramas de tabaco del producto THS 2.2 Menthol que desee si está en el grupo 1 o fumar la cantidad de cigarrillos mentolados convencionales que desee si está en el grupo 2. Sin embargo, no tendrá libre acceso a los cigarrillos mentolados convencionales ni al producto THS 2.2 Menthol. El personal del estudio distribuirá los cigarrillos mentolados convencionales y las ramas de tabaco del producto THS 2.2 Menthol cuando usted lo solicite, uno a la vez. No está permitido fumar durante la realización de los procedimientos del estudio. El día 6, no podrá fumar ni usar el producto THS 2.2 Menthol antes de que se hayan realizado todos los análisis de laboratorio y todas las pruebas para evaluar la función pulmonar completa. En este estudio no se permite fumar fuera del edificio, por lo tanto, se le pedirá que fume sus cigarrillos mentolados convencionales o que use el producto THS 2.2 Menthol en una cabina para fumar dentro del edificio. La cabina está construida en vidrio y tiene

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espacio para 8 personas a la vez. La cabina utiliza filtros para contener el humo y evitar que salga de allí. Un miembro del personal le explicará cómo usar las cabinas y cómo apagar sus cigarrillos mentolados convencionales o desechar las ramas de tabaco del THS 2.2 Menthol cuando haya terminado de usarlas o de fumar.

Si es asignado al grupo 3, se requiere abstinencia completa de fumar durante todo el estudio, desde el día 1 hasta el día 91. Durante el período de internamiento que abarca desde el día 1 hasta el día 6, el personal del centro supervisará cuidadosamente a todos los participantes de la investigación del grupo 3 para detectar posibles signos y síntomas de la abstinencia de nicotina. Durante este período, no puede usar ningún medicamento para ayudar a la abstinencia de fumar ni usar ningún producto que contenga tabaco/nicotina. Se le brindará ayuda psicológica durante el período de abstinencia de fumar.

Al final del período de internamiento cuando usted sea dado de alta del centro el día 6, se le indicará que continúe con el producto/régimen al cual fue asignado en un contexto ambulatorio durante 86 días; esto es, continuar usando el producto THS 2.2 Menthol, si fue asignado al grupo 1, y continuar fumando los cigarrillos mentolados convencionales, si fue asignado al grupo 2; o bien, abstenerse de fumar, si fue asignado al grupo 3. Tendrá que registrar todos los días en un diario electrónico cualquier uso del producto THS 2.2 Menthol, cigarrillos convencionales (mentolados o no mentolados), terapia de reemplazo de la nicotina, por ejemplo, goma de mascar de nicotina u otros productos que contengan nicotina/tabaco. Si durante el período ambulatorio usa cualquier otro producto que contenga nicotina/tabaco distinto del producto/régimen asignado, no se le pedirá que deje de participar en el estudio.

Durante el período ambulatorio, no habrá restricciones con respecto a fumar/al uso del producto, excepto durante las tres visitas al centro (visitas de los días 30, 60 y 90), cuando se permitirá el uso del producto desde el ingreso por la mañana antes de las 8:30 a. m. hasta las 11:00 p. m. de los días 30, 60 y 90. Los días 31 y 61, se permitirá el uso del producto desde las 6:30 a. m. en adelante. El día 91, se permitirá el uso del producto después de que se hayan realizado algunas evaluaciones (por ejemplo, la Escala Minnesota de abstinencia de la nicotina [*Minnesota Nicotine Withdrawal Scale*] y cuestionarios sobre la tos, evaluaciones de la función pulmonar completa) hasta el momento del alta del día 91. Si fue asignado al grupo de cigarrillos mentolados convencionales o el grupo de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol.

Si fue asignado al grupo del producto THS 2.2 Menthol, el personal del centro le dará instrucciones sobre cómo desechar las ramas de tabaco del producto THS Menthol.

Si es asignado al grupo 1 (grupo del producto THS 2.2 Menthol), durante el período ambulatorio tendrá que visitar el centro aproximadamente cada 2 semanas para que se le suministren nuevos paquetes de ramas de tabaco del producto THS 2.2 Menthol. Durante esta visita no se realizará ninguna otra evaluación. Cuando venga a la clínica para las visitas de los días 30, 60 y 90, deberá devolver al centro los paquetes vacíos, sin usar y abiertos de las ramas de tabaco del producto THS 2.2 Menthol sin usar, así

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como las piezas del producto THS 2.2 Menthol (es decir, las ramas de tabaco del THS, la boquilla, el cargador y los accesorios del THS).

Si en cualquier momento durante el estudio desea dejar de fumar, el personal del estudio le ayudará con esta decisión y lo referirá a los servicios médicos. Permanecerá en el estudio y completará las visitas y los procedimientos restantes. Sin embargo, puede decidir retirarse del estudio en cualquier momento.

SELECCIÓN

Acudirá a la clínica para una visita de selección en la que se determinará si usted es elegible para participar en este estudio. La visita de selección tendrá lugar como máximo 28 días antes de la admisión en el centro. Se espera que llegue al centro de investigación habiendo ayunado durante al menos 10 horas, que se requiere para determinados análisis de sangre. Antes de que se realicen las pruebas y los procedimientos relacionados con el estudio, se le pedirá que lea y firme este documento de consentimiento. Para determinar si reúne los requisitos para participar en este estudio, se llevarán a cabo las pruebas y los procedimientos siguientes:

- Se le asesorará sobre el riesgo de fumar (entrevista breve de conformidad con las recomendaciones del Servicio de Salud Pública [*Public Health Service*] de los Estados Unidos), y se le brindará asesoramiento para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se reunirá información demográfica sobre usted (edad, sexo, raza, grupo étnico).
- Se le harán preguntas sobre sus antecedentes médicos y sus condiciones clínicas actuales.
- Se le harán preguntas sobre cualquier medicamento que haya estado usando en el pasado y cualquier medicamento que use actualmente. Se le indicará qué medicamentos podrá usar mientras esté en el estudio.
- Se le preguntará cómo se siente.
- Se le harán preguntas acerca de sus antecedentes de tabaquismo.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o antes (para ello, responderá el cuestionario de Prochaska "Etapa de cambio" [*Stage of Change*]).
- Se le preguntará si está preparado para cumplir con los procedimientos descritos en el protocolo del estudio (por ejemplo, si está preparado para abstenerse de fumar durante un máximo de 91 días).
- Se le preguntará qué marca de cigarrillos mentolados normales fuma.
- Se le realizará una exploración física, se medirán los signos vitales (pulso, presión arterial y frecuencia respiratoria estando previamente en posición de decúbito supino durante al menos 5 minutos) y se medirá la estatura y el peso para calcular el índice de masa corporal (IMC).
- Se le realizará un ECG (electrocardiograma, un trazado indoloro del ritmo cardíaco). Un ECG muestra el patrón de los latidos del corazón. Es posible que a los varones se les deba afeitar el vello del pecho antes de los ECG para que los parches se adhieran a la piel. Las mujeres no podrán usar sostén.
- Se obtendrán muestras de sangre y de orina para realizar análisis de laboratorio clínico, después de un período de ayuno de 10 horas.

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- A las mujeres también se les realizará una prueba de embarazo en orina.
- Se realizarán pruebas para la detección de VIH (SIDA) y hepatitis (de una muestra de sangre), drogas ilegales (de una muestra de orina), cotinina (de una muestra de orina) y alcohol (de una muestra de sangre o de una prueba respiratoria).
- Durante esta visita, el personal del estudio llevará a cabo una demostración del producto THS 2.2 Menthol.
- Se realizará una radiografía del pecho si no se ha realizado una dentro de los 6 meses anteriores. La radiografía se llevará a cabo en una unidad de radiología (rayos X). La radiografía del pecho consta de dos imágenes radiográficas que se toman en ángulos diferentes.
- Se le pedirá que sople dentro de una máquina llamada espirómetro. Esto se realizará antes y después de inhalar un broncodilatador de acción rápida (medicamento para "abrir" los bronquios). Esta máquina medirá qué tan bien funcionan los pulmones. Esta prueba se realizará al menos una hora después de fumar.
- Se le pedirá que complete un cuestionario específico sobre la dependencia de la nicotina (Prueba de Fagerstrom de dependencia de nicotina [*Fagerstrom Test for Nicotine Dependence*]).
- Se le entregarán dos formularios de consentimiento informado adicionales para subestudios opcionales. Su participación en el estudio principal no depende de su decisión de firmar o no estos formularios de consentimiento informado.

El virus de inmunodeficiencia humana (VIH) es el virus que puede causar el síndrome de inmunodeficiencia adquirida (SIDA). Para poder reunir los requisitos para participar en este estudio, primero debe obtener un resultado negativo en la prueba de anticuerpos contra el VIH. Los anticuerpos son sustancias que produce el sistema inmunitario del cuerpo para combatir infecciones. Un análisis de sangre puede demostrar si usted ha estado expuesto o está infectado con el VIH. La decisión de aceptar realizarse la prueba de VIH es voluntaria y solamente usted puede tomarla. Sin embargo, si elige no realizarse la prueba de VIH, no podrá participar en este estudio. La prueba de anticuerpos contra el VIH se realizará de forma confidencial. Un resultado VIH positivo no significa que usted tenga VIH o SIDA, así como una prueba con resultado negativo no significa que usted no esté infectado porque puede tardar hasta tres meses que la prueba indique la infección. Los resultados positivos de las pruebas de hepatitis y VIH deben informarse a un organismo de salud local. Esta es la obligación legal de los profesionales de la salud en este estado.

Si no reúne los requisitos para participar en el estudio según los resultados de otros procedimientos de selección, o si usted no completa la visita de selección, es posible que estas pruebas de VIH no se realicen.

Se le comunicará que puede continuar fumando su marca preferida de cigarrillos mentolados convencionales.

Se le permitirá participar en el estudio a discreción del médico del estudio si los

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resultados de los análisis de laboratorio de la selección del estudio y de otras evaluaciones realizadas tanto en la selección como el día de la admisión (día -2) son satisfactorios. Es posible que sea necesario repetir los procedimientos de selección para que pueda ingresar en este estudio. Se le comunicarán las restricciones del estudio y cuándo debe regresar a la unidad de investigación para comenzar el estudio.

Es posible que sea necesario repetir algunos procedimientos de selección en el ingreso para confirmar la elegibilidad. Estas pruebas pueden mostrar una modificación desde la selección que indique un cambio en su salud o bienestar físico que quizá haga que usted no sea elegible en el momento del ingreso.

Si después de completar los procedimientos de selección usted reúne los requisitos para el estudio, deberá comprar sus propios cigarrillos mentolados convencionales de la marca que prefiera antes de la admisión. El día -2, deberá entregarle al personal del estudio la cantidad de paquetes que considere que podría fumar durante 9 días más 4 paquetes adicionales. El patrocinador no proporcionará los cigarrillos mentolados convencionales. Los paquetes sin usar o usados parcialmente se le devolverán cuando sea dado de alta del centro.

PROCEDIMIENTOS DEL ESTUDIO

Periódicamente durante el estudio, se medirán los signos vitales (presión arterial, pulso) y se realizarán ECG. También se le harán preguntas para saber cómo se siente y si ha usado algún medicamento. Además, las muestras de sangre y/o de orina obtenidas en este estudio pueden usarse para realizar análisis de laboratorio clínico de rutina, análisis del medicamento del estudio, constituyentes del humo seleccionados, biomarcadores, marcadores de riesgo, niveles de nicotina y monóxido de carbono. También se le pedirá que complete varios cuestionarios sobre los cigarrillos, el hábito de fumar, la preferencia de fumar, su percepción de los riesgos asociados con el uso del producto THS 2.2 Menthol y la abstinencia de fumar. Consulte a continuación la lista de evaluaciones que deberá realizar cada día.

En función del diseño del estudio, es posible que sea seleccionado como suplente para este estudio. En este caso, puede seguir los procedimientos de las secciones Admisión y Visita inicial (día -1 y día 0), pero no será asignado a ningún grupo del estudio ni participará en el resto del estudio.

Día -2 (admisión/ingreso)

El día -2 concurrirá al centro de investigación para comenzar su internamiento en el centro de investigación.

Si es elegible:

- Se le realizará una exploración física, y se medirá su peso y cintura. Se calculará el índice de masa corporal.
- Se obtendrán muestras de orina para realizar análisis de laboratorio (pruebas para



detectar el uso de drogas ilegales y una prueba de embarazo en orina para las mujeres).

- Se le preguntará cómo se siente.
- Se le harán preguntas sobre cualquier medicamento que esté usando actualmente y sus condiciones clínicas actuales.
- Recibirá información sobre el riesgo de fumar/asesoramiento para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se le preguntará acerca de sus antecedentes de tabaquismo.
- Se realizará una prueba de alcohol (en una muestra de orina o una prueba respiratoria).
- Se le preguntará si está preparado para cumplir con los procedimientos descritos en el protocolo del estudio (por ejemplo, si está preparado para abstenerse de fumar durante un máximo de 91 días).
- Se realizará una prueba de medición de monóxido de carbono en el aliento (medición de la cantidad de monóxido de carbono en el aliento).
- Se medirán los signos vitales (presión arterial, frecuencia del pulso, frecuencia respiratoria).
- Se identificará la marca de cigarrillo mentolado convencional que fuma actualmente (deberá entregarle al personal del centro su propio suministro de cigarrillos mentolados convencionales para el período de internamiento. Tomarán una fotografía del paquete).
- Antes de la prueba del producto THS 2.2 Menthol, se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o antes (para ello, responderá el cuestionario de Prochaska "Etapa de cambio").
- Realizará una prueba del producto THS 2.2 Menthol (solamente después de que se confirme un resultado negativo en la prueba de embarazo en las mujeres). Como último procedimiento de los criterios de elegibilidad, probará el producto THS 2.2 Menthol (usando como máximo 3 ramas de tabaco mentolado). A continuación, se le preguntará si está listo para usar el producto THS 2.2 Menthol durante el tiempo que dure el estudio, si fue asignado de forma aleatoria al grupo 1.
- Si cumple con todos los criterios de elegibilidad, será inscrito en el estudio.
- Después de confirmar su inscripción en el estudio, se le preguntará a qué producto preferiría ser asignado de forma aleatoria, si pudiera elegir el grupo del estudio (preguntas de preferencia de producto). Sin embargo, tenga en cuenta que, en realidad, el grupo del estudio en el que ingrese se decidirá de forma aleatoria y usted no puede elegirlo. Si prefiere ser asignado de forma aleatoria al grupo SA, se le pedirá nuevamente que responda el cuestionario de Prochaska "Etapa de cambio". Según su respuesta, es posible que sea retirado del estudio.

Continuará fumando sus propios cigarrillos mentolados convencionales hasta las 11:00 p. m.

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- Desde las 10:00 a. m. hasta las 2:00 p. m., usted orinará en recipientes desechables que luego le entregará al personal del centro. El personal del centro le proporcionará información detallada sobre el método de obtención de orina. La orina obtenida se usará para analizar biomarcadores de exposición y marcadores de riesgo.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizarán pruebas de determinación de monóxido de carbono en el aliento cuatro veces por día; la primera prueba se llevará a cabo 15 minutos antes de la primera vez que fume y las otras pruebas tendrán lugar entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m.
- Se medirán los signos vitales (presión arterial, frecuencia cardíaca y frecuencia respiratoria).
- Cuestionario de impulsos de fumar (deseo de fumar) (*Questionnaire of Smoking Urges*): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos (*Modified Cigarette Evaluation Questionnaire*): se le pedirá que complete un cuestionario para evaluar el producto THS 2.2 Menthol y los cigarrillos mentolados convencionales.
- Se le pedirá que complete dos cuestionarios para evaluar su conducta actual y anterior con respecto al hábito de fumar (Cuestionario de factores de riesgo conductuales [*Behavioral Risk Factor Questionnaire*] y Cuestionario sobre el hábito de fumar [*Smoking Questionnaire*]) y datos complementarios sobre la conducta relacionada con el hábito de fumar.
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (una medición de los niveles de monóxido de carbono en la sangre), entre las 8:00 y las 9:30 p. m.
- Se deberán juntar todas las colillas de cigarrillos mentolados convencionales que haya fumado para llevar un control.

Visita inicial, día 0

Lo despertarán temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio.

- Comienzo de la obtención de orina de 24 horas del día 0 (cada vez que orine deberá hacerlo en recipientes desechables que luego le entregará al personal del centro). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará una prueba de determinación de monóxido de carbono en el aliento (cuatro veces por día; la primera prueba se llevará a cabo 15 minutos antes de la primera vez que fume y las otras pruebas tendrán lugar entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m.).
- Se obtendrán muestras de sangre para el día 0 de la siguiente manera:

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- Una muestra para hematología, bioquímica clínica y marcadores de riesgo: se obtendrá después de al menos 10 horas de ayuno.
- Una muestra de sangre para el almacenamiento en banco de material biológico a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (si da su consentimiento para esta muestra) (debe realizarse después de al menos 10 horas de ayuno).
- Una muestra para almacenamiento en banco de material biológico para realizar análisis adicionales de investigación transcriptómica (si dio su consentimiento para una muestra para pruebas genéticas) (se debe realizar después de al menos 10 horas de ayuno).
- Una muestra para medir los oxisteroles ("colesterol") en la sangre (se debe realizar después de al menos 10 horas de ayuno).
- Una muestra para medir la carboxihemoglobina (una medida de la concentración de monóxido de carbono en la sangre) (antes de las pruebas para evaluar la función pulmonar completa)
- Una muestra para medir la actividad de la enzima CYP2A6, una entidad biológica involucrada en el metabolismo de la nicotina en la sangre (se debe realizar antes de fumar).
- Una muestra para medir la actividad de la enzima CYP1A2 (que interviene en el metabolismo de la cafeína), entre las 4:00 y las 5:30 p. m., 6 horas después de haber ingerido un comprimido de cafeína.
- Una muestra para medir la carboxihemoglobina (una medición de los niveles de monóxido de carbono en la sangre), entre las 8:00 y las 9:30 p. m.
- Una muestra para medir los niveles de nicotina y cotinina en la sangre, entre las 8:00 y las 9:30 p. m.
- Tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 240 ml de agua (para medir la enzima CYP1A2), entre las 10:00 y las 11:30 a. m.
- Se realizará una prueba de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes de fumar.
- Se obtendrá una muestra de orina para realizar análisis de seguridad.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Se realizará una topografía del fumador (un procedimiento indoloro para evaluar la conducta con respecto al hábito de fumar) solamente si se le proporciona el dispositivo HST SODIM® (un dispositivo que mide la forma individual de fumar de una persona). Tenga en cuenta que si le entregan el dispositivo HST SODIM®, debe usarlo todas las veces que fume el día 0.
- Cuestionario sobre topografía del fumador: si se le entrega el dispositivo HST SODIM® también se le pedirá que complete un cuestionario para evaluar el uso del HST en rituales relacionados con el hábito de fumar entre las 8:00 y las 11:00 p. m.

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- Evaluación de la tos (se le pedirá que complete un cuestionario en el que se evalúa la tos) y la Escala Minnesota de abstinencia de la nicotina (se le pedirá que complete un cuestionario para evaluar los signos y síntomas de la abstinencia). Los cuestionarios se deben completar antes de fumar, pero no más tarde de las 10:00 a. m.
- Se le pedirá que complete un cuestionario para evaluar el producto (Cuestionario modificado de evaluación de cigarrillos) y un cuestionario para evaluar su deseo de fumar (Cuestionario de impulsos de fumar), entre las 8:00 y las 11:00 p. m.
- Obtención de células epiteliales nasales (obteniones de células de la nariz) y de una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalles si firma el formulario de consentimiento informado correspondiente a cada uno.
- Se recogerán todas las colillas de los cigarrillos mentolados convencionales que haya fumado para llevar un control.

Días 1 a 5 del período de exposición

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio

- Antes de las 6:30 a. m. del día 1, se le comunicará a qué grupo del estudio ha sido asignado de forma aleatoria.
- Recibirá asistencia para abstenerse de fumar, si fuese necesario (solamente el grupo de abstinencia de fumar).
- Se realizará la obtención de orina de 24 horas desde la mañana del día 1 hasta la mañana del día 6 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del centro). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- El día 1 finaliza la obtención de orina de 24 horas que había comenzado el día 0. La orina obtenida durante las 24 horas se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo, además se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para almacenarlas a largo plazo en un banco de material biológico y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- La orina obtenida durante las 24 horas de los días 2, 3, 4 y 5 se usará para analizar los biomarcadores de exposición y la creatinina.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrán muestras de sangre para realizar lo siguiente:
 1. Medición de la carboxihemoglobina: días 1 a 4, una muestra de sangre al anochecer, entre las 8:00 y las 9:30 p. m., cada día. Día 5, una muestra de sangre dentro de los 15 minutos anteriores al primer uso del producto del día, entre las 8:00 y las 9:30 a. m., para los sujetos del grupo de abstinencia de fumar, seguida de tres muestras de sangre adicionales entre las 12:00 y la

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1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m., para todos los sujetos.

2. Medición de la nicotina/cotina: días 1 a 4, una muestra de sangre al anochecer, entre las 8:00 y las 9:30 p. m., cada día. El día 5, solamente para los grupos del producto THS 2.2 Menthol y de cigarrillos mentolados convencionales, una muestra de sangre dentro de los 15 minutos anteriores al primer uso del producto de ese día seguida de ocho muestras a intervalos de 2 horas. Para los sujetos asignados de forma aleatoria al grupo de abstinencia de fumar, el día 5 se obtendrá una muestra de sangre por la noche, entre las 8:00 y las 9:30 p. m.
- Solamente el día 5, se obtendrá una muestra de sangre para medir la actividad de la enzima CYP1A2 (que interviene en el metabolismo de la cafeína): la muestra se obtendrá entre las 4:00 y las 5:30 p. m., 6 horas después de haber tomado un comprimido de cafeína.
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento, cuatro veces al día: la primera prueba se realizará 15 minutos antes del primer cigarrillo o uso del producto, entre las 8:00 y las 9:30 de la mañana, para los sujetos del grupo de abstinencia de fumar; las otras pruebas se llevarán a cabo aproximadamente entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m. y las 8:00 y las 9:30 p. m., para todos los sujetos (días 1 a 5).
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: días 1 a 5).
- Evaluación de la tos (se le pedirá que complete un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (se le pedirá que complete un cuestionario para evaluar los signos y síntomas de la abstinencia) (debe realizarse antes de fumar, no más tarde de las 10:00 a. m., los días 1 a 5).
- Se le pedirá que complete un cuestionario para evaluar el producto (Cuestionario modificado de evaluación de cigarrillos) y un cuestionario para evaluar su deseo de fumar (Cuestionario de impulsos de fumar), entre las 8:00 y las 11:00 p. m. de los días 1 a 5.
- Solamente el día 4, se le pedirá que complete un cuestionario sobre su estado socioeconómico. Se le hará una serie de preguntas relacionadas con su educación, estado ocupacional, cantidad de personas que viven con usted e ingreso anual de su casa. Puede responder todas las preguntas que desee.
- Solamente el día 4, se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales y se le proporcionó el dispositivo HST SODIM®).
- Solamente el día 5, se le pedirá que complete dos cuestionarios para evaluar su conducta actual y anterior con respecto al hábito de fumar (Cuestionario de factores de riesgo conductuales y Cuestionario sobre el hábito de fumar) y datos complementarios con respecto a la conducta relacionada con el hábito de fumar.
- Solamente el día 5, tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 240 ml de agua (para medir la enzima CYP1A2), entre las 10:00 y las 11:30 a. m.

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- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que si se le entrega el dispositivo HST SODIM®, y está en el grupo del producto THS 2.2 Menthol y de cigarrillos mentolados convencionales, debe utilizarlo para todos los usos de producto (días 1 a 4).

Fumar los cigarrillos mentolados convencionales o usar el producto THS 2.2 Menthol está permitido de 6:30 a. m. a 11:00 p. m., pero no durante los procedimientos del estudio. Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas del producto THS 2.2 Menthol y las colillas de los cigarrillos mentolados convencionales (días 1 a 5). En el grupo del producto THS 2.2 Menthol, se le pedirá que recoja todos los restos de tabaco usados en los frascos exclusivos que le entregará el personal.

Día 6 (alta)

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio

- Recibirá asistencia para abstenerse de fumar, si fuese necesario (solamente el grupo 3).
- Se obtendrán muestras de sangre (que incluyen muestras para medir un perfil de nicotina: se extraerán dos muestras de sangre, la primera tendrá lugar 20 horas después de la hora de inicio del primer uso del producto, el día 5, y la segunda será 24 horas después del inicio del primer uso del producto, el día 5. En el caso del grupo de abstinencia de fumar, se extraerá una sola muestra de sangre entre las 8:00 y las 9:30 a. m.).
- El día 6 finaliza la obtención de orina de 24 horas que comenzó el día 5. Esta muestra se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo; además, se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para el almacenamiento en banco de material biológico a largo plazo y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- Se obtendrán muestras de sangre y de orina para realizar análisis de laboratorio (hematología, bioquímica clínica, después de un período de al menos 10 horas de ayuno), un análisis de orina general y una prueba de embarazo en orina para todas las mujeres.
- Se obtendrán muestras de sangre para realizar análisis de marcadores de riesgo (después de al menos 10 horas de ayuno).
- Se obtendrán muestras de sangre para almacenamiento a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.

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- Se obtendrá una muestra de sangre para almacenamiento a largo plazo para realizar análisis adicionales de transcriptómica (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Se obtendrá una muestra de sangre para medir los oxiesteroles (después de un período de al menos 10 horas de ayuno).
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (antes de la prueba para evaluar la función pulmonar completa).
- Se obtendrá una muestra de sangre para medir la actividad de la enzima CYP2A6 (se debe realizar antes de fumar).
- Se realizará una exploración física que incluye la medición del peso y el cálculo del índice de masa corporal.
- Completará un cuestionario de Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia) (se debe realizar antes del uso del producto, pero no más tarde de las 10:00 a. m.).
- Se realizarán pruebas de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes del uso del producto.
- Se realizará una prueba de determinación de monóxido de carbono en el aliento.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria).
- Se realizará un electrocardiograma (un trazado indoloro del ritmo y la frecuencia cardíaca).
- Se le asesorará sobre el riesgo de fumar y sobre la importancia de dejar de fumar, y se le proporcionará información sobre el producto THS 2.2 Menthol.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrán células epiteliales nasales (obteniones de células de la nariz) y una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalle si firma el formulario de consentimiento informado correspondiente a cada uno.
- Será dado de alta del centro.

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas del producto THS 2.2 Menthol y las colillas de los cigarrillos mentolados convencionales. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Antes ser dado de alta del centro, se le entregará un diario electrónico que usará para registrar cualquier uso de las ramas de tabaco del producto THS 2.2 Menthol, los

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cigarrillos convencionales (mentolados y no mentolados), los productos de terapia de sustitución de la nicotina o el uso de otros productos que contengan nicotina/tabaco. Todos los participantes, incluidos los del grupo 3, deben completar este diario todos los días desde el momento del alta el día 6 hasta el momento del alta el día 91. Recibirá capacitación para usar este diario electrónico.

Después del alta el día 6, se le indicará que continúe utilizando el producto/régimen que se le asignó en su casa durante 86 días. Si se lo asignó al grupo SA, es posible que se le proporcione terapia de sustitución de la nicotina (no se permitirá el uso de ningún otro producto medicinal para dejar de fumar) si el investigador lo considera necesario o si usted lo solicita.

Visita del día 30 (desde el ingreso antes de las 8:30 a. m. del día 30 hasta la salida el día 31) y visita del día 60 (desde el ingreso antes de las 8:30 a. m. hasta la salida el día 61)

Se permitirá fumar o usar el producto en el centro desde el ingreso hasta aproximadamente las 11:00 p. m. de los días 30 y 60 y desde las 6:30 a. m. de los días 31 y 61. No hay restricciones con respecto a fumar/al uso del producto antes del ingreso al centro. Si fue asignado al grupo de cigarrillos mentolados convencionales o al de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol. Durante las visitas de los días 30 y 60, se le pedirá que continúe completando el diario electrónico todos los días.

Se le pedirá que traiga suficiente suministro del producto que ha estado usando para cubrir su estadía durante el internamiento. Se le proporcionarán ramas de tabaco del producto THS 2.2 Menthol durante su estadía en la clínica. Si se lo asigna al grupo del producto THS 2.2, tendrá que traer todos los paquetes vacíos y las ramas de tabaco de producto THS 2.2 sin usar. También deberá traer el dispositivo THS 2.2 (con todas las piezas: las boquillas, el cargador, la herramienta de limpieza, la fuente de energía principal y el cable USB) y el diario electrónico.

Durante los días 30 y 60, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará la obtención de orina de 24 horas desde la mañana de los días 30 y 60 hasta la mañana de los días 31 y 61 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del estudio). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Prueba de embarazo en orina (para las mujeres).
- Obtención de una muestra de sangre para medir la carboxihemoglobina.
- Obtención de una muestra de sangre para medir la nicotina y la cotinina en la

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sangre.

- Exploración física que incluye la medición del peso y el cálculo del índice de masa corporal.
- Se le realizará un ECG (electrocardiograma, un trazado indoloro del ritmo cardíaco).
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Cuestionario de impulsos de fumar (deseo de fumar): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos: se le pedirá que complete un cuestionario para evaluar el producto.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o menos (respondiendo el cuestionario de Prochaska "Etapa de cambio").
- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que el dispositivo HST SODIM® debe utilizarse para todo los usos de producto de los grupos de THS 2.2 Menthol y cigarrillos mentolados convencionales durante un período de 4 horas cada día y solamente con el producto al cual usted ha sido asignado.
- Se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®).

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Días 31 y 61

Durante estos días, usted puede comenzar a fumar/usar el producto desde las 6:30 a. m.

Durante los días 31 y 61, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo 3).
- Preguntas sobre cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Obtención de muestras de sangre para realizar análisis de laboratorio (hematología, bioquímica clínica) y análisis de marcadores de riesgo después de un período de al menos 10 horas de ayuno.
- Finalización de la obtención de orina de 24 horas desde el día 30 o el día 60. La orina obtenida durante 24 horas se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo.

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- Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia).
- Análisis de orina de seguridad.
- Recibirá asesoramiento sobre el riesgo de fumar/para dejar de fumar e información sobre el producto THS 2.2 Menthol.

Visita del día 90 (desde el ingreso antes de las 8:30 a. m. del día 90 hasta el alta el día 91)

Se le pedirá que traiga suficientes ramas de tabaco, de las que ha estado usando, para su estadía en la clínica. Se reabastecerán las ramas de tabaco del producto THS 2.2 durante su estadía en la clínica.

Si es asignado al grupo del producto THS 2.2, para esta visita tendrá que traer todos los paquetes vacíos o sin usar y las ramas de tabaco de producto THS 2.2 sin usar. También deberá traer el dispositivo de calentamiento de tabaco (con todas las piezas: las boquillas, el cargador, la herramienta de limpieza, la fuente de energía principal y el cable USB) y el diario electrónico. Dejará todos estos suministros en el centro el día 91, cuando sea dado de alta.

Se permitirá fumar o usar el producto en el centro desde el ingreso hasta aproximadamente las 11:00 p. m. y el día 91 solamente después de que se haya realizado la medición de la actividad de la enzima CYP2A6 y la espirometría. No hay restricciones para fumar/usar el producto antes del ingreso al centro. Si fue asignado al grupo de cigarrillos mentolados convencionales o al de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol.

Durante la visita del día 90, se le pedirá que continúe completando el diario electrónico todos los días.

Día 90

Durante el día 90, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que el dispositivo HST SODIM® debe usarse para todo los usos de producto de los grupos de THS 2.2 Menthol y cigarrillos mentolados convencionales durante un período de 4 horas cada día y solamente con el

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producto al cual usted ha sido asignado.

- Se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®).
- Se realizará la obtención de orina de 24 horas desde la mañana del día 90 hasta la mañana del día 91 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del estudio). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 200 ml de agua.
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento.
- Obtención de una muestra de sangre para medir la carboxihemoglobina.
- Obtención de una muestra de sangre para medir la nicotina y la cotinina en la sangre.
- Obtención de una muestra de sangre para medir la actividad de la enzima CYP1A2, que se realizará 6 horas después de que haya tomado el comprimido de cafeína.
- Obtención de células epiteliales nasales (obteniones de células de la nariz) y de una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalle si firma el formulario de consentimiento informado correspondiente a cada uno.
- Cuestionario de impulsos de fumar (deseo de fumar): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos: se le pedirá que complete un cuestionario para evaluar el producto.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o menos (respondiendo el cuestionario de Prochaska "Etapa de cambio").
- Se le pedirá que complete un cuestionario específico sobre la dependencia de la nicotina (Prueba de Fagerstrom de dependencia de nicotina).

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Día 91

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio.

Durante este día, se realizarán los siguientes procedimientos:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).

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- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrá una muestra de sangre para medir la actividad de la enzima CYP2A6 en la sangre. Esta muestra de sangre se obtendrá antes de que fume o use el producto THS 2.2 Menthol.
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (antes de la prueba de la función pulmonar completa).
- Se realizarán pruebas de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes del uso del producto.
- Obtención de muestras de sangre para realizar análisis de laboratorio (hematología, bioquímica clínica) y marcadores de riesgo, después de un período de al menos 10 horas de ayuno.
- Una muestra de sangre para medir los oxisteroles, después de un período de al menos 10 horas de ayuno.
- Un análisis de seguridad en orina, y una prueba de embarazo en orina para todas las mujeres.
- Exploración física que incluye la medición del peso, el perímetro de la cintura y el cálculo del índice de masa corporal.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Se le realizará un electrocardiograma, un trazado indoloro del ritmo cardíaco.
- Obtención de muestras de sangre para el almacenamiento a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Obtención de una muestra de sangre para almacenamiento a largo plazo para realizar análisis adicionales de transcriptómica (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Finalización de la obtención de orina de 24 horas que comenzó el día 90. Esta muestra se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo; además, se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para el almacenamiento en banco de material biológico a largo plazo y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- Comienzo de la obtención de orina de 4 horas el día 91 (a partir de las 10:00 a. m. y durante un período de 4 horas, cada vez que orine, lo hará en recipientes desechables que luego le entregará al personal del centro). La orina obtenida se usará para analizar los biomarcadores de exposición y los marcadores de riesgo.



- Recibirá asesoramiento sobre el riesgo de fumar/para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se le pedirá que complete una Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia).
- Antes de abandonar el centro deberá entregarle al personal del centro el dispositivo THS 2.2 Menthol, las ramas de tabaco del producto THS 2.2 sin usar (si está en el grupo 1) y el diario electrónico.

Período de seguimiento de seguridad:

Habrà un período de seguimiento de seguridad durante 28 días después de la última visita del estudio planificada (alta del día 91 o finalización anticipada). Si se retira del estudio de forma anticipada, ingresará en el período de seguimiento el día que se retire.

Si participó en la prueba del producto del día -2, pero no fue inscrito en el estudio, aun así ingresará en el período de seguimiento de 28 días.

Durante este período de seguimiento de seguridad, debe comunicarle al centro cualquier problema médico nuevo que experimente. El personal del centro también se comunicará con usted para realizar un seguimiento de cualquier problema médico que usted comunique durante el estudio o durante el período de seguimiento que no se haya resuelto después de haber sido dado de alta del centro.

Procedimientos de retirada

Si usted se retira de forma anticipada del estudio por cualquier motivo, es posible que se le pida que complete los análisis de laboratorio y los procedimientos descritos anteriormente en la sección Día 6.

No se le permitirá traer su propia comida o bebida al centro de investigación. Las comidas se servirán según los cronogramas predeterminados para este estudio. Si tiene cualquier pregunta relacionada con las comidas, hable con su médico del estudio. Habrá disponible bocadillos ligeros, frutas y verduras crudas sin restricciones en cualquier momento durante el período de internamiento. El consumo de agua también está permitido sin restricciones. Se les proporcionará a los participantes de todos los grupos del estudio un menú estándar y un cronograma de comidas.

Muestras de sangre y orina

Durante todo el estudio, se extraerán aproximadamente 316 ml de sangre (alrededor de 1 taza y $\frac{1}{4}$). A modo de comparación, una donación estándar de sangre en un centro de obtención de sangre, una vez dentro de cualquier período de 56 días, representa aproximadamente 500 ml (alrededor de 2 tazas) de sangre.

El personal capacitado y cualificado del centro será responsable de la obtención de las muestras de sangre. El volumen total máximo de sangre extraída incluye 40 ml para los

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análisis de seguridad y repetidos, 30 ml para almacenamiento a largo plazo de muestras en un banco de material biológico para realizar análisis adicionales de biomarcadores de exposición en el cuerpo y marcadores de riesgo (solamente si se otorgan los consentimientos adicionales) y 15 ml para el almacenamiento a largo plazo de las muestras en un banco de material biológico para realizar análisis adicionales de transcriptómica (solamente si se otorgan los consentimientos adicionales).

Es posible que se requieran muestras de sangre adicionales si alguno de sus valores de laboratorio fuera anormal. Es posible que sea necesario hacer más de un intento para obtener una muestra de sangre. Pueden obtenerse muestras de sangre adicionales durante el estudio si el médico del estudio lo considera necesario para supervisar su salud. Las muestras de sangre obtenidas se analizarán mediante el uso de métodos validados, a excepción de los oxiesteroides que serán analizados en un laboratorio correctamente equipado. El laboratorio de análisis designado será responsable de conservar las muestras durante este período y de su posterior destrucción. En todo momento durante el estudio, se mantendrá la seguridad de su información personal y su identidad permanecerá anónima.

Las muestras de sangre y de orina para los análisis de laboratorio de seguridad se evaluarán en el centro o en un laboratorio designado, y se conservarán durante aproximadamente 2 meses y luego serán destruidas.

Todas las muestras de sangre y de orina para la medición de biomarcadores de exposición y marcadores de riesgo se analizarán y se conservarán según la documentación relevante del laboratorio.

Las muestras que proporcione solamente se usarán para los objetivos relacionados con el estudio, y no se realizará ningún otro análisis que no sean los análisis relacionados con el estudio que se han descrito en esta hoja de información sin la aprobación suya y del comité de ética.

Todos los datos reunidos se almacenarán durante el tiempo que sea necesario según las leyes, regulaciones y normas vigentes, para garantizar que los datos estén disponibles para las inspecciones del estudio que realicen las autoridades normativas, así como para garantizar la integridad del estudio.

Si bien las investigaciones futuras en las que se usen sus muestras pueden derivar en el desarrollo de nuevos productos, usted no recibirá ninguna compensación por estos productos nuevos. Al aceptar este uso, usted renuncia a todo reclamo de dinero que los investigadores obtengan del uso comercial o de otro tipo de estas muestras.

Responsabilidades del participante de la investigación

Como participante de una investigación, se le pedirá que complete los procedimientos de este estudio, que acuda a la clínica del estudio para hacer todas las visitas programadas, que siga las instrucciones señaladas en este formulario de consentimiento informado y que notifique al médico del estudio si cambia algún dato relacionado con su salud o su disponibilidad para participar en este estudio.

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**Restricciones generales**

- Para evitar la contaminación cruzada de distintos productos, el grupo 1 (THS 2.2 Menthol) y el grupo 2 (cigarrillos mentolados convencionales) deben usar los productos a los que han sido asignado en cabinas para fumar separadas. El grupo 3 (abstinencia de fumar) no podrá estar en la zona de fumadores.
- No debe haber usado medicamentos recetados NI medicamentos de venta libre durante 4 semanas antes del inicio del estudio ni durante todo el estudio, incluido el período de seguimiento de seguridad. Comuníquelo al médico del estudio cualquier medicamento (recetado, de venta libre, suplementos a base de hierbas/vitaminas) que esté tomando. Él podrá decirle si está permitido o no que los tome durante el estudio.
- No debe haber participado en un estudio de investigación dentro de los últimos 3 meses.
- No debe haber donado sangre o plasma (por ejemplo, plasmaféresis) dentro de los 3 meses anteriores a la admisión.

Si es asignado al grupo 1, no podrá fumar ningún cigarrillo mentolado convencional ni usar ningún producto que contenga tabaco/nicotina (incluida la terapia de reemplazo de la nicotina) desde el día 1 (6:30 a. m.) hasta el momento del alta el día 6.

Restricciones alimenticias

- Se servirán comidas y bocadillos estandarizados (y controlados en calorías) a intervalos regulares durante su internamiento en la clínica, excepto cuando se requiera ayuno o se indique lo contrario.
- Durante el período de internamiento, no se permitirá el consumo de carne asada o frita, carnes precocidas ahumadas (por ejemplo, atún, jamón, carne de vaca en conserva y carnes), tocino ahumado y salchichas.
- Durante el período de internamiento, no se permitirá el consumo de alcohol, brócoli, coles de Bruselas, coliflor, jugo de pomelo o toronja, y alimentos y bebidas que contengan xantina (café, té, chocolate, cacao, mate, guaraná, etc.).
- No está permitido el consumo de bebidas que contengan quinina (por ejemplo, agua tónica) durante el período de internamiento.
- Un día antes de la visita del día 90, no debe consumir jugo de pomelo o toronja ni productos que contengan pomelo o toronja, ni bebidas que contengan quinina (por ejemplo, agua tónica). No se permite el consumo de bebidas alcohólicas, coles de Bruselas, coliflor, carne asada, alimentos o bebidas que contengan xantinas (por ejemplo, café, té, chocolate, cacao, mate, guaraná) en el centro durante la visita ambulatoria.
- No se le permitirá traer su propia comida o bebida al centro de investigación.
- Las comidas se servirán según los cronogramas predeterminados para este estudio. Si tiene cualquier pregunta relacionada con las comidas, hable con su médico del estudio.
- Habrá disponible bocadillos ligeros, frutas y verduras crudas sin restricciones en cualquier momento durante el período de internamiento.

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- El consumo de agua también está permitido sin restricciones.
- Se les proporcionará a los participantes de todos los grupos del estudio un menú estándar y un cronograma de comidas.

RIESGOS Y MOLESTIAS

Es posible que haya riesgos para usted si participa en este estudio. Como consumidor de tabaco, los riesgos asociados con el uso del tipo de producto con tabaco que consume normalmente seguirán siendo los mismos. En este momento, el uso del producto THS 2.2 Menthol no proporciona ningún riesgo menor de desarrollar enfermedades relacionadas con el tabaco que los cigarrillos de la marca que fuma habitualmente.

Fumar provoca adicción y causa a los fumadores graves enfermedades mortales como cáncer de pulmón, enfermedades pulmonares y cardiovasculares (enfermedad cardíaca), además de otras enfermedades graves. Ningún cigarrillo es seguro. Lo único que se ha demostrado que reduce el riesgo de desarrollar enfermedades relacionadas con fumar en fumadores es dejar de fumar. A pesar de los riesgos atribuibles al tabaquismo, algunos fumadores tienen dificultades para dejar de fumar o deciden seguir fumando.

Fumar tabaco es perjudicial, y los estudios médicos han demostrado que fumar tabaco es una de las causas principales de muchas enfermedades. Si acepta, durante las visitas le proporcionaremos más información sobre los riesgos relacionados con fumar y le asesoraremos para dejar de fumar.

También puede experimentar síntomas de abstinencia y antojos durante todo el estudio, según el grupo al que fue asignado. Es posible que durante este período experimente algunos síntomas conocidos de abstinencia de la nicotina, entre ellos: antojos de tabaco, irritación, ira, problemas de concentración, dolores de cabeza, fatiga, estreñimiento, inquietud, insomnio, mareos y ansiedad.

El uso particular del producto THS 2.2 Menthol puede implicar riesgos para el sujeto (o el embrión o feto, si la participante está embarazada o puede quedar embarazada). Actualmente, estos riesgos son imprevisibles.

Si tiene seguro médico privado, puede que tenga que hacerle saber a los aseguradores que usted tiene intenciones de participar en un proyecto de investigación para que puedan comunicarle si esto afectará su seguro.

Existe la posibilidad de que las distintas pruebas que se llevan a cabo durante el estudio permitan descubrir un problema médico del cual usted no tenía conocimiento previo. Si esto sucede, el médico de la investigación hará los arreglos necesarios para que reciba un tratamiento adecuado y/o, con su permiso, lo derivará a su médico de atención primaria.



No se le permitirá usar terapia de sustitución de la nicotina ni otros productos de ayuda para dejar de fumar durante su estadía en la clínica.

Tenga en cuenta que todos los médicos que trabajan en el centro de investigación están capacitados y cuentan con certificación en procedimientos de soporte vital avanzado para tratar cualquier emergencia médica. Los enfermeros y otro personal de la clínica también están capacitados en procedimientos de emergencia.

En estudios clínicos anteriores, se han evaluado versiones anteriores del producto THS 2.2 Menthol, que no han demostrado preocupaciones con respecto a la seguridad. Sin embargo, al participar en este estudio, es posible que usted experimente algunos eventos (incluidos, entre otros, dolor de cabeza, dolor causado por la extracción de sangre y mareos). Si sufre alguno de estos efectos secundarios o cualquier otro efecto secundario, debe buscar ayuda médica y comunicarse con el médico o el personal del estudio.

Es posible que haya otros riesgos para usted mientras participa en este estudio. Puede experimentar algunas molestias asociadas con el uso del producto THS 2.2 Menthol que no se han comunicado con anterioridad. Es posible que haya algunos riesgos desconocidos o poco frecuentes e imprevisibles asociados con el uso de este producto del estudio, incluso reacción alérgica o interacción con fármacos y medicamentos que esté usando. Además, pueden presentarse otros efectos secundarios graves desconocidos, incluso la muerte.

Todas estas ocurrencias se registrarán, y los investigadores y enfermeros le explicarán determinadas medidas para limitarlas. Durante el desarrollo del estudio, un equipo de investigadores y enfermeros capacitados supervisará su salud y su seguridad.

Si experimenta alguno de los efectos secundarios mencionados más arriba u otros síntomas, debe comunicárselo al médico o al personal del estudio de inmediato. Si no le proporciona al médico o al personal del estudio esta información relacionada con cualquier efecto secundario, al participar en este estudio podría ocasionarse involuntariamente un daño.

Si tiene preguntas sobre los signos o síntomas de los efectos secundarios que leyó en este formulario de consentimiento, hágaselas al médico del estudio.

Para reducir la posibilidad de lesiones, siempre use el dispositivo de acuerdo con las instrucciones del fabricante. Las advertencias y las instrucciones de seguridad incluidas en el Manual del usuario no cubren todos los posibles problemas médicos y las situaciones que podrían ocurrir. Consulte el Manual del usuario para obtener más información.

RIESGOS DE LOS PROCEDIMIENTOS DEL ESTUDIO

Durante la obtención de las muestras de sangre, es posible que experimente dolor y/o la formación de moretones en el sitio en que se inserta la aguja/el catéter o el lugar donde se coloca el brazalete para medir la presión arterial. Aunque es raro, puede haber

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formación localizada de coágulos, daños en los nervios e infecciones. También puede experimentar sensación de desvanecimiento y/o desmayos durante la extracción de sangre o poco después.

Los electrodos del ECG pueden causar una reacción en la piel, como enrojecimiento o picazón. Usted también puede presentar molestias en la piel y/o pérdida de vello localizadas asociadas con la colocación de los electrodos del ECG.

Radiografías: si es necesario realizar una radiografía del pecho durante el proceso de selección para este estudio, la exposición a la radiación de una radiografía equivale a aproximadamente 3 días de exposición a la radiación ambiental natural.

Espirometría: para este procedimiento se usará un broncodilatador de acción rápida (medicamento para abrir los bronquios). Es posible que haya un riesgo pequeño de una reacción adversa a este medicamento (como la sensación de que el corazón late más rápido [palpitaciones] o temblores/sacudidas leves). Debe comunicarle al médico del estudio de inmediato cualquier síntoma que pueda experimentar mientras usa este medicamento. Los procedimientos se llevarán a cabo según las normas internacional y científicamente aceptadas.

RIESGOS DESCONOCIDOS/IMPREVISIBLES

Además de los riesgos mencionados anteriormente, pueden existir algunos riesgos desconocidos, poco frecuentes e imprevisibles asociados al uso de estos productos, que incluyen reacciones alérgicas graves o que ponen en riesgo la vida, o interacciones inesperadas con otro medicamento. Se le comunicará oportunamente, tanto en forma oral como escrita, toda nueva información, hallazgo o cambio en la forma en que se llevará a cabo la investigación que pudiera influir sobre su deseo de seguir participando en este estudio.

Si sufre una lesión, un efecto malo o cualquier otra experiencia de salud inusual durante este estudio, debe comunicarse con el médico o el personal del estudio de inmediato.

RIESGOS PARA UN BEBÉ EN GESTACIÓN

Riesgos en el embarazo/para el feto: se sabe que los efectos de fumar para un niño en gestación son dañinos. No debe estar embarazada para participar en este estudio. Es importante que use los siguientes métodos anticonceptivos adecuados durante todo el estudio y hasta la finalización del período de seguimiento de seguridad, y que las mujeres no queden embarazadas ni amamanten a un bebé.

- Dispositivo o sistema intrauterino (DIU).
- Uso establecido de métodos hormonales orales/inyectables/implantables/transdérmicos.
- Métodos anticonceptivos de barrera.
 - Preservativos ○ capuchones oclusivos (diafragma) con espuma/gel/película/supositorio espermicida.

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- Pareja(s) que se haya(n) realizado una vasectomía.
- Abstinencia verdadera (la abstinencia periódica y el coito interrumpido no son métodos eficaces).

No es necesario usar anticonceptivos, si se ha practicado histerectomía, ligadura de trompas, ovariectomía bilateral o si es posmenopáusica. El estado posmenopáusico se define como mujeres que no han tenido ciclos menstruales durante más de 12 meses. Se debe realizar una prueba de la hormona foliculoestimulante, cuyo resultado debe estar dentro de los límites aceptables.

Si cree que ha quedado embarazada durante el estudio, es importante que se lo comunique al médico del estudio de inmediato. Si queda embarazada o cree que puede estar embarazada, será retirada del estudio y el médico del estudio la derivará para que reciba atención obstétrica. El costo de esa atención será responsabilidad suya. Es posible que el médico del estudio le pida hacer un seguimiento de su embarazo, y le informará al patrocinador y al Comité de Revisión Independiente (*Independent Review Board*, IRB) sobre el embarazo y su desenlace.

BENEFICIOS

La participación en este estudio tiene fines exclusivamente de investigación y no mejorará su salud ni tratará cualquier problema médico que pueda tener. Puede beneficiarse por la realización de las exploraciones físicas. Los resultados de los análisis de laboratorio realizados durante la visita de selección se pondrán a su disposición si lo solicita. Sin embargo, si usted no reúne los requisitos para participar en el estudio según otros procedimientos de selección, es posible que no se realicen algunos análisis de laboratorio.

Este estudio se realiza únicamente con fines de investigación. No hay ningún beneficio directo para usted por participar en el estudio, excepto que recibirá un examen de la salud y asesoramiento para dejar de fumar. Los resultados del estudio ayudarán al patrocinador a comprender mejor la seguridad del producto THS 2.2 Menthol y qué tan bien el cuerpo absorbe la nicotina que contiene el producto. Esta información puede ayudar a otras personas en el futuro.

ALTERNATIVAS AL TRATAMIENTO

En este estudio, no se administra ningún medicamento en estudio. Por lo tanto, no hay ningún tratamiento alternativo que corresponda como parte de este estudio. Sin embargo, si decide que desea dejar de fumar, el personal del estudio le proporcionará información sobre cómo buscar ayuda para hacerlo.

COSTO

Participar en este estudio de investigación no implica ningún costo. El producto THS 2.2 Menthol, los procedimientos relacionados con el estudio y las visitas del estudio se proporcionarán sin cargo para usted ni para su compañía de seguros.

COMPENSACIÓN POR PARTICIPAR EN ESTE ESTUDIO

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Será compensado por participar en este estudio de investigación según lo detallado a continuación. Esta compensación es por su tiempo y los inconvenientes causados. Recibirá una compensación según el siguiente programa.

Programa de compensación

Visita de selección	-0-
Visita de selección para realizar una radiografía del pecho	\$50.00
Noches de internamiento en el centro de investigación (11 noches x \$250.00)	\$2750.00
Visita extendida como paciente ambulatorio (3 visitas x \$200)	\$600.00
Diarios (por semana), 14 semanas x \$100	\$1400.00
Finalización del estudio	\$720.00
TOTAL	\$5520.00

La compensación total del estudio completo será de \$5520. Si elige retirarse del estudio de investigación, recibirá una compensación solamente por la parte del estudio que haya completado según lo detallado más arriba. Si Covance debe comprarle cigarrillos mentolados convencionales porque se le acabaron durante el período de confinamiento, la cantidad que se haya gastado se deducirá del total de su compensación.

Si se retira del estudio de forma anticipada debido a un evento médico importante o si el patrocinador cancela el estudio, recibirá una compensación de un importe correspondiente a la parte de la compensación del estudio completo en función de la cantidad de visitas que haya realizado.

Si es seleccionado como un suplente y no es seleccionado para participar en el estudio, recibirá una compensación de \$250.00 para cada noche. Si como suplente obtiene un resultado positivo en las pruebas de detección de cualquier droga no autorizada o de alcohol, no recibirá ninguna compensación.

Todos los participantes de la investigación recibirán su compensación dentro de los 21 días posteriores a la finalización de su participación en el estudio.

Si participa en este estudio, acepta que no será considerado un empleado de Covance o de Philip Morris Products S.A.

No se deducen impuestos de su cheque. Usted es responsable del pago de cualquier impuesto estatal, federal o de seguro social. Deberá proporcionarle a Covance su número de seguro social o número de identificación fiscal, si lo tiene. Si recibe de Covance más de \$600 en un año calendario, se le entregará el formulario de impuestos 1099 en el siguiente mes de enero. Covance comunica el dinero que usted recibe al

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Servicio de Impuestos Internos (*Internal Revenue Service*, IRS).

Si no tiene un número de seguro social o un número de identificación fiscal, el Servicio de Impuestos Internos (IRS) le exige a Covance deducir el 30% de su compensación. Deberá seguir la normativa del IRS para determinar si es elegible para recibir un reembolso, o bien, comunicarse con un contador especializado en impuestos para que le ayude.

DERECHO A RETIRARSE O SER RETIRADO DEL ESTUDIO

Su participación en este estudio es voluntaria. Usted es libre de retirarse de este estudio en cualquier momento; sin embargo, debe comunicarle inmediatamente al médico del estudio si tiene previsto retirarse. Su decisión de participar en este estudio o de retirarse de él no influirá sobre la disponibilidad de su atención médica futura y no implicará sanciones ni pérdida de los beneficios a los que tenga derecho. Puede retirarse de este estudio en cualquier momento. Puede retirar su consentimiento para usar y divulgar su información en cualquier momento. Si usted retira su consentimiento, no podrá seguir participando en este estudio. Si por cualquier motivo se retira o abandona el estudio de forma anticipada, se le pedirá que complete los procedimientos del alta del día 6.

El patrocinador del estudio o el médico a cargo del estudio pueden retirarlo de este estudio sin su consentimiento por cualquier motivo, entre otros:

- El patrocinador o el médico del estudio consideran que un problema médico o una circunstancia puede poner en peligro su bienestar o la integridad del estudio.
- Si usted no sigue las instrucciones del equipo del estudio.
- Si el patrocinador y/o los médicos que participan en el estudio detienen el estudio antes de su finalización o el patrocinador pide que se lo retire del estudio.

CONFIDENCIALIDAD

Si acepta participar en el estudio de investigación, el personal del estudio reunirá, registrará y almacenará información sobre su identidad, salud y participación.

El patrocinador y sus representantes, la Administración de Alimentos y Medicamentos (FDA) de los Estados Unidos, otras autoridades de salud y el Comité de Revisión Independiente MidLands pueden inspeccionar sus registros médicos en papel o en forma electrónica que posiblemente incluyan su nombre, dirección y otra información personal que permita identificarlo. Si fuera necesario, se pueden copiar todos sus registros médicos o parte de ellos durante estas inspecciones.

Los resultados de este estudio de investigación pueden presentarse en conferencias o pueden incluirse en publicaciones. Sin embargo, usted no será identificado

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personalmente en ninguna presentación o publicación.

Debido a la necesidad de usar información según lo observado más arriba, no se puede garantizar la confidencialidad absoluta.

Habrà una descripción de este ensayo clínico disponible en www.ClinicalTrials.gov, según lo exigen las leyes de los Estados Unidos. Este sitio web no incluirà información que pueda identificarlo. A lo sumo, incluirà un resumen de los resultados. Puede consultar este sitio web en cualquier momento.

CONFIDENCIALIDAD COMERCIAL

La información y todo material o artículo que se le entregue relacionado con el estudio o durante el estudio, como información que permite identificar la unidad de investigación, el patrocinador, cualquier producto del estudio y/o el tipo de estudio que se está realizando, se deberá considerar información comercial confidencial de Covance y el patrocinador del estudio. Por supuesto que usted es libre de analizar esta información confidencial con otras personas, como su médico o sus amigos y familiares, para considerar la posibilidad de participar o no en este estudio o en cualquier momento en que analice su atención médica presente o futura, o sus derechos. Sin embargo, se prohíbe la distribución de información comercial confidencial según lo descrito más arriba en cualquier medio de comunicación o su publicación en Internet.

¿QUIÉN ORGANIZA ESTA INVESTIGACIÓN?

La empresa que patrocina este estudio es Philip Morris Products S.A., Suiza (incluidos los agentes, contratistas o consultores).

¿QUIÉN HA REVISADO EL ESTUDIO?

El Comité de Revisión Independiente MidLands (MLIRB) ha revisado los objetivos y la realización propuesta del estudio principal.

EN CASO DE LESIONES

Su seguridad es la principal preocupación de cada miembro del personal. Comuníquese con el personal del estudio lo antes posible si tiene efectos secundarios o lesiones. El número de teléfono de Covance Dallas Clinical Research Unit es 214-920-9053.

Covance le proporcionará tratamiento médico inmediato, sin costo para usted, por los efectos secundarios o las lesiones que hayan sido causadas por participar en este estudio. Los gastos médicos en los que incurra por cualquier lesión relacionada con la investigación, diferentes de los costos del tratamiento médico inmediato, serán responsabilidad suya o de un tercero pagador. No se le impide que busque obtener compensación por una lesión relacionada con negligencia, fallas, o culpa de las personas involucradas en la investigación.

Al firmar este formulario de consentimiento, usted **NO RENUNCIA** a ninguno de sus

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derechos legales.

CONTACTO DE EMERGENCIA

Si durante el estudio experimenta cualquier problema médico o sufre una lesión relacionada con la investigación, comuníquese con el médico del estudio llamando al número de teléfono que figura en la página uno de este documento de consentimiento. Si busca atención de emergencia o requiere internamiento, comuníquelo al médico que lo trate que usted está participando en un estudio de investigación dirigido por el médico del estudio que se menciona en la página uno de este documento.

PERSONAS QUE DEBEN CONTACTARSE PARA PREGUNTAS, PREOCUPACIONES O QUEJAS

Si tiene alguna pregunta o algún problema, si cree que puede haber sufrido una lesión relacionada con la investigación, o si tiene preguntas sobre la disponibilidad de atención médica, debe comunicarse con el Dr. William Lewis llamando al 214-920-9053.

Si tiene preguntas sobre sus derechos, preguntas generales, quejas o preocupaciones sobre esta investigación, o preguntas sobre sus derechos como una persona que participa en este estudio, llame al Comité de Revisión Independiente MidLands (MLIRB) al (913) 385-1414 o al (800) 636-4445. Si en cualquier momento durante o después de su participación en esta investigación, le gustaría recibir información u ofrecer datos sobre su experiencia en la investigación, puede llamar al IRB MidLands al número que figura más arriba o puede visitar el sitio web del IRB MidLands en www.mlirb.com y enviarnos sus comentarios. En cualquier caso, no tiene que darnos su nombre, si no lo desea.

Usted tiene derecho a hacer cualquier pregunta sobre los peligros potenciales y/o conocidos de este estudio en cualquier momento. Si tiene cualquier pregunta sobre su participación en este estudio, o si en cualquier momento cree haber experimentado una lesión relacionada con la investigación o una reacción al medicamento del estudio, comuníquese con el Dr. William Lewis llamando al 214-920-9053.

DERECHOS LEGALES

Al firmar este formulario de consentimiento, usted no perderá ninguno de sus derechos legales a los que tenga derecho de otro modo.

DECLARACIÓN DE CIERRE

Usted ha leído cuidadosamente la información anterior. Además, ha recibido respuestas satisfactorias a todas las preguntas que ha hecho y firma voluntariamente este formulario de consentimiento. Recibirá una copia del documento de consentimiento informado firmado. Por la presente, acepta voluntariamente participar en este estudio.

Puede retirar este consentimiento en cualquier momento.

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**NOTIFICACIÓN AL MÉDICO DE CABECERA**

Después de que se hayan realizado todas las pruebas de elegibilidad y se haya determinado que usted es apto para ingresar en el estudio, si lo desea, le comunicaremos a su médico particular que está participando en este estudio de investigación. Marque su preferencia a continuación.

- ☐ Sí, quiero que el médico del estudio le informe a mi médico particular acerca de mi participación en este estudio.

Nombre, dirección y número de teléfono del médico particular

- ☐ No, no quiero que el médico del estudio le informe a mi médico particular acerca de mi participación en este estudio.
- ☐ No tengo un médico particular.

**FIRMAS****Lea el párrafo siguiente en voz alta a la persona que obtiene el consentimiento.**

- He leído la información anterior en un idioma que comprendo bien.
- Me han explicado el contenido y el significado de esta información.
- He tenido la oportunidad de hacer mis preguntas en privado así como reunirme con un médico del estudio para analizar este estudio.
- He hecho al personal las preguntas que pueda haber tenido y he tenido tiempo suficiente para decidir si quiero participar en este estudio.
- Por medio del presente, acepto y me ofrezco voluntariamente a participar en este estudio, y autorizo el uso y la divulgación de información médica sobre mi persona.
- También acepto que se realicen las pruebas de VIH descritas en este documento.
- Dono voluntaria y libremente todas las muestras de sangre y orina para la investigación descrita más arriba, y por el presente, renuncio a todos los derechos de propiedad, título e interés que pueda tener sobre esas muestras.
- Acepto mantener la confidencialidad de toda la información relacionada con el producto del estudio (THS 2.2 Menthol), que incluye el diseño del producto, las especificaciones y el método de funcionamiento.

Nombre del participante en letra de imprenta

Firma del participante

Fecha

Hora

Nombre en letra de imprenta de la
persona que realiza el análisis del
consentimiento informado
y la verificación del alfabetismoFirma de la persona que
realiza el análisis del
consentimiento informado
y la verificación del alfabetismo

Fecha

Hora

He recibido una copia firmada y fechada del formulario de consentimiento de este estudio para que la guarde.**Su firma****Fecha**

Para completar únicamente por el personal de Covance:

QC'd by _____

Date

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**AUTORIZACIÓN Y CONSENTIMIENTO PARA USAR Y DIVULGAR
INFORMACIÓN DE SALUD PROTEGIDA PARA INVESTIGACIÓN**

Durante su participación en este estudio de investigación, el médico y el personal del estudio obtendrán o generarán información médica personal sobre usted (por ejemplo, registros médicos y resultados de todas las pruebas, los exámenes o los procedimientos que se realicen mientras participa en el estudio) y la registrarán en documentos del estudio. El médico del estudio conservará esta información médica de salud personal en sus registros relacionados con el estudio (a los que haremos referencia como "sus registros del estudio"). Además, el médico del estudio puede obtener, e incluir en sus registros, información sobre su salud y/o sus problemas físicos o mentales pasados, presentes y/o futuros. Es posible que el médico del estudio le pida que firme otra autorización para obtener parte o todos sus registros médicos de su médico. Sus registros del estudio pueden incluir otra información personal (como el número de seguro social, números de registros médicos, fecha de nacimiento, etc.), que podrían usarse para identificarlo. La información de la salud que podría identificarlo se llama "información de salud protegida" (*protected health information*, PHI).

Cuando corresponda de acuerdo con las leyes federales (la "Norma de privacidad") u otras leyes vigentes, su PHI creada u obtenida durante este estudio de investigación no podrá "usarse" para realizar la investigación ni "divulgarse" (entregarse a ninguna persona o entidad) con fines de investigación sin su permiso o consentimiento. Este permiso y consentimiento se llama "autorización". Por lo tanto, usted no puede participar en este estudio a menos que dé su permiso para usar y divulgar su PHI firmando esta autorización. Al firmar, está aceptando permitir al médico y al personal del estudio el uso de su PHI para llevar a cabo este estudio.

Al firmar esta autorización, usted también está aceptando permitir al médico y al personal del estudio que divulguen su PHI a las personas y los grupos que se describen a continuación:

- El patrocinador de este estudio (PATROCINADOR) y cualquier persona que trabaje en representación del patrocinador para llevar a cabo este estudio (a quienes se hace referencia como "el patrocinador"). El patrocinador analizará y evaluará la PHI, y puede usarla para desarrollar nuevas pruebas, procedimientos y productos comerciales. El personal del estudio le asignará un código numérico y/o letras a sus registros, lo que significa que usted no será habitualmente identificado en los registros que se envíen al patrocinador. Sin embargo, el patrocinador podrá ver sus registros completos del estudio o recibir información relacionada con las muestras que lo identifican. Además, el patrocinador puede visitar el centro del estudio para supervisar la forma en que se está efectuando el estudio, y puede revisar su PHI durante estas visitas, para asegurarse de que la información sea correcta.
- El Comité de Revisión Independiente ("IRB") puede tener acceso a su PHI en relación con sus responsabilidades como Comité de Revisión Institucional.

El médico o el patrocinador del estudio pueden divulgar su PHI a la Administración de

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Alimentos y Medicamentos ("FDA") de los Estados Unidos u organismos reguladores similares en Estados Unidos y/o países extranjeros.

Estas divulgaciones también ayudan a asegurar que la información relacionada con la investigación esté disponible para todas las partes que puedan necesitarla con fines de investigación.

Excepto las divulgaciones descritas anteriormente, su PHI no se compartirá con otras personas o entidades a menos que lo requiera la ley. Si su PHI se entrega a las partes mencionadas anteriormente y/o a otras personas o entidades que no están obligadas a cumplir las leyes vigentes, es posible que su PHI ya no esté protegida por estas leyes y posiblemente se use o divulgue de maneras diferentes a las descritas aquí.

Tiene derecho a ver y a hacer copias de su PHI. Sin embargo, al firmar este documento, usted acepta que no podrá ver ni copiar su PHI, ya sea total o parcialmente, hasta que el patrocinador haya completado todo el trabajo relacionado con este estudio. En ese momento, podrá pedir ver sus registros.

Esta autorización no tiene fecha de vencimiento a partir de la fecha en que la firme, a menos que la revoque (cancele o retire) antes.

Tiene derecho a revocar su autorización en cualquier momento. Si la revoca, su PHI dejará de usarse para este estudio, excepto en la medida en que las partes vinculadas con la investigación ya hubieran actuado teniendo en cuenta su autorización o necesiten la información para completar análisis e informes de esta investigación. Para revocar su autorización, debe escribir al médico del estudio a la dirección que figura en la primera página de este formulario, manifestando que revoca su autorización para el uso y la divulgación de la información de salud protegida. Si revoca esta autorización, no podrá continuar participando en este estudio.

Recibirá una copia de esta autorización fechada y firmada después de que la haya firmado.

Firma del sujeto

Fecha

Nombre del sujeto en letra de imprenta

Firma de la persona que obtiene la autorización

Fecha

Nombre en letra de imprenta de la persona que obtiene la autorización

Para completar únicamente por el personal de Covance:

QC'd by _____

Date _____

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APPROVED BY
APR 22 2014
MLIRB
Medical Research & Development

**AUTORIZACIÓN Y CONSENTIMIENTO INFORMADO PARA PARTICIPAR
EN UNA INVESTIGACIÓN CLÍNICA**

Título del estudio. Estudio aleatorizado, controlado, abierto, multicéntrico, de 3 grupos paralelos, para demostrar las reducciones en la exposición a constituyentes del humo seleccionados en fumadores aparentemente sanos que cambian al sistema de calentamiento de tabaco mentolado 2.2 (THS 2.2 Menthol) o dejan de fumar, en comparación con continuar usando cigarrillos mentolados convencionales, durante 5 días en internamiento y 86 días más en un contexto ambulatorio.

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Número de selección del sujeto:	<input type="text"/>
Investigador principal: (médico del estudio)	Covance Dallas Site Dr. William Lewis
Dirección del centro de investigación:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Número de teléfono:	Covance Dallas Site Teléfono: 214-920-9053
Número de teléfono las 24 horas:	Covance Dallas Site Teléfono: 972-955-5373
Patrocinador:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Suiza

Se le invita a participar en un estudio de investigación. Sin embargo, antes de que dé su consentimiento para participar en el estudio, lea lo siguiente y haga todas las preguntas que sean necesarias para asegurarnos de que comprende qué implicará su participación. Se le entregará una copia de este formulario de consentimiento informado para que se la lleve a su casa.

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INTRODUCCIÓN

Su participación en este estudio de investigación es voluntaria. Es importante que lea y comprenda la siguiente explicación de los procedimientos propuestos. Este formulario de consentimiento informado describe el objetivo, los procedimientos, los beneficios, las alternativas, los riesgos conocidos o reconocidos, las molestias y las precauciones del estudio, e incluye la duración y la naturaleza de su participación. También describe su derecho a retirarse del estudio en cualquier momento. Para ingresar en el estudio, debe firmar y fechar este formulario de consentimiento en calidad de participante de la investigación.

Tenga en cuenta lo siguiente: si no es absolutamente sincero con el médico respecto a sus antecedentes de salud, que incluyen alergias y uso de medicamentos, podría perjudicarse al participar en este estudio.

NATURALEZA Y OBJETIVO DEL ESTUDIO

El patrocinador de este estudio es Philip Morris Products, un fabricante de productos que contienen tabaco. El patrocinador está desarrollando un enfoque alternativo a los cigarrillos convencionales (normales) a través de un producto que posiblemente permita reducir algunos riesgos de las enfermedades relacionadas con el tabaco.

El sistema de calentamiento de tabaco mentolado 2.2 (*tobacco heating system*, THS 2.2 Menthol) es un producto en fase de investigación que se está desarrollando como una alternativa en lugar de los cigarrillos convencionales que no ha sido aprobada por la Administración de Alimentos y Medicamentos (*Food and Drug Administration*, FDA) de los Estados Unidos.

Se cree que al calentar el tabaco, en lugar de quemarlo como ocurre con los cigarrillos convencionales, es posible que se reduzcan los efectos perjudiciales de fumar.

No se ha demostrado que el producto THS 2.2 Menthol reduzca las enfermedades relacionadas con el consumo de tabaco y usted no debe suponer que los riesgos asociados al uso del producto THS 2.2 Menthol sean diferentes de los que produce fumar cigarrillos comunes.

El objetivo general de este estudio es reunir información sobre el uso del producto en fase de investigación THS 2.2 Menthol cuando se proporciona a los participantes de una investigación que están hospitalizados en el centro de investigación y luego en un contexto ambulatorio. El estudio de investigación comparará el uso del producto THS 2.2 Menthol con los cigarrillos mentolados convencionales y la abstinencia de fumar. Durante este estudio se medirán varios biomarcadores de exposición presentes en el cuerpo y marcadores de riesgo. El estudio también obtendrá información de seguridad relacionada con el uso del producto THS 2.2 Menthol.

Los biomarcadores de exposición son sustancias que se miden en el cuerpo como el resultado del consumo de otra sustancia (como el humo de cigarrillo). Por ejemplo,

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cuando fuma usted inhala monóxido de carbono. El monóxido de carbono se une a determinada parte de los glóbulos rojos llamada hemoglobina. El monóxido de carbono puede reemplazar al oxígeno presente en los glóbulos rojos. En este estudio, se medirá el nivel de monóxido de carbono unido a la hemoglobina y se hará referencia a este nivel como un biomarcador de exposición al monóxido de carbono.

Un marcador de riesgo es una característica biológica que se asocia a un mayor riesgo de desarrollar determinadas enfermedades o infecciones. Para comprender las diferencias biológicas (fisiológicas) entre el producto THS 2.2 Menthol, los cigarrillos mentolados convencionales y la abstinencia de fumar, se tomarán otras mediciones, incluidos los marcadores de irritación (inflamación) de la nariz y de los tipos de colesterol en la sangre.

Los objetivos adicionales de este estudio de investigación son comprender mejor lo que el cuerpo hace con la nicotina y sus productos de degradación (incluidas las enzimas que intervienen en la degradación) en los fumadores que cambian de cigarrillos mentolados convencionales al producto THS 2.2 Menthol en comparación con los fumadores que continúan fumando cigarrillos mentolados convencionales. Además, en este estudio se evaluarán los patrones y las preferencias del hábito de fumar (es decir, la topografía del fumador), el uso del producto y los efectos subjetivos relacionados.

Este estudio tiene solamente fines de investigación y no está destinado a tratar ningún problema médico.

También se le invitará a participar en dos subestudios adicionales, opcionales. En uno, se realizarán análisis farmacogenómicos de sus muestras biológicas. No está obligado a participar en ninguno de estos dos subestudios opcionales. Se le entregarán 2 formularios de consentimiento informado separados para estos subestudios adicionales. **Si no desea participar en estos subestudios adicionales, su participación en este estudio de investigación principal no se verá afectada.**

Covance Clinical Research Unit Inc. recibe un pago por evaluar el producto en fase de investigación THS 2.2 Menthol. Los médicos de este estudio trabajan para Covance, pero no tienen ningún interés económico en los resultados de este estudio.

¿QUÉ PRODUCTO SE ESTÁ EVALUANDO?

El producto que desarrolla el patrocinador y que se evalúa en este estudio se llama THS 2.2 Menthol. Este producto mantiene el calentamiento del tabaco a una temperatura mucho más baja que la que se observa en los cigarrillos normales (convencionales). El producto THS 2.2 Menthol consta de los siguientes componentes: las ramas de tabaco mentolado para el THS (ramas de tabaco mentolado), la boquilla, el cargador, una herramienta para limpieza, una fuente de energía principal y un cable USB.

El dispositivo de calentamiento de tabaco comprende todos estos componentes en el producto THS 2.2 Menthol, excepto las ramas de tabaco mentolado. La función de la

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boquilla es calentar la rama de tabaco mentolado, lo que produce un aerosol que recibe el usuario. El calentamiento eléctrico funciona con una batería interna que genera energía durante aproximadamente 6 minutos (lo que alcanza para el uso completo de una sola rama de tabaco). A diferencia de los cigarrillos normales, las ramas de tabaco mentolado no se queman durante el consumo y el largo sigue siendo el mismo después de su uso.

En este momento, es importante que usted comprenda que no se ha demostrado que el producto THS 2.2 Menthol reduzca las enfermedades relacionadas con el tabaco y no debe suponer que los riesgos asociados con el uso de este producto sean diferentes de los que se relacionan con fumar cigarrillos normales.

SELECCIÓN DE LOS PARTICIPANTES DE LA INVESTIGACIÓN

Se le invita a participar en este estudio porque usted es una fumadora o un fumador aparentemente sano que tiene más de 22 años de edad y fuma cigarrillos mentolados convencionales, y posiblemente sea apto para participar en este estudio.

Si está pensando seriamente en dejar de fumar en los próximos 6 meses, usted no califica para participar en este estudio. Sin embargo, debe estar dispuesto(a) a abstenerse de fumar durante el estudio si resulta seleccionado al azar para el grupo de abstinencia del tabaco.

Si es una mujer, no debe estar embarazada ni amamantando. Si decide participar en este estudio, se le pedirá que use métodos anticonceptivos adecuados durante el estudio.

Es importante que responda completamente y con sinceridad todas las preguntas de selección. Debe comunicar todas las enfermedades y alergias actuales y anteriores, así como todos los medicamentos que esté usando, incluidos los medicamentos recetados y de venta libre. **Si no revela toda la información sobre sus antecedentes médicos, cualquier problema médico que usted tenga y los medicamentos que ha usado, podría ser peligroso para su salud.**

En este estudio de investigación multicéntrico, se asignarán de forma aleatoria 160 participantes.

DURACIÓN DEL ESTUDIO

La duración de su participación en este estudio es de aproximadamente 123 a 150 días incluido el período de selección. Se realizará una visita de selección como máximo 28 días (día -30 a día -3) antes de la admisión en el centro de Investigación (para determinar si usted reúne los requisitos para este estudio de investigación). Este estudio requiere un internamiento de 9 días y 8 noches (día -2 a día 6) en el centro de investigación seguida de 3 visitas los días 30 a 31, 60 a 61 y 90 a 91. Cada visita constará de 2 días consecutivos (con estadía de 1 noche en cada visita) en el centro. En la visita del día 30, ingresará al centro antes de las 8:30 a. m. y saldrá después de que se hayan realizado todas las evaluaciones del día 31. En la visita del día 60, ingresará al centro antes de las 8:30 a. m. del día 60 y saldrá después de que se hayan

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realizado todas las evaluaciones del día 61. En la visita del día 90, ingresará al centro antes de las 8:30 a. m. del día 90 y será dado de alta el día 91, después de que se hayan realizado todas las evaluaciones.

Después del día 91, habrá un período de seguimiento de seguridad de 28 días durante el cual debe comunicarle al personal del centro cualquier problema médico nuevo que tenga. El personal del centro también se comunicará con usted para realizar un seguimiento de cualquier problema médico que usted comunique durante el estudio o durante el período de seguimiento que no se haya resuelto después de haber sido dado de alta del centro, el día 91.

Durante el estudio, desde la selección hasta la finalización del período de seguimiento de seguridad, siempre debe comunicarse con el centro antes de tomar cualquier medicamento (recetado o de venta libre).

DISEÑO DEL ESTUDIO

Este estudio de investigación será de "diseño abierto". Esto significa que usted, el médico del estudio y el patrocinador sabrán qué productos recibe. Una vez que se determine que usted reúne los requisitos para el estudio, será asignado de forma aleatoria (al azar, como cuando se arroja una moneda al aire) a 1 de los siguientes 3 grupos del estudio. Esto se realizará el día 0. El día 1, se le comunicará el grupo al cual fue asignado. Usted no podrá elegir el grupo al cual es asignado.

Usted tiene un 50% de probabilidades de estar en el grupo 1 y un 25% de estar en el grupo 2 o 3.

- **Grupo 1:** grupo del sistema de calentamiento de tabaco, THS 2.2 Menthol (80 participantes).
- **Grupo 2:** grupo de cigarrillos mentolados convencionales (40 participantes).
- **Grupo 3:** grupo de abstinencia de fumar (40 participantes).

Si es asignado al grupo 1 o 2, se le permitirá fumar durante el período de internamiento (desde el día 1 hasta el momento en que sea dado de alta del centro, el día 6) entre las 6:30 a. m. y las 11:00 p. m. cada día. Durante este período, usted puede usar la cantidad de ramas de tabaco del producto THS 2.2 Menthol que desee si está en el grupo 1 o fumar la cantidad de cigarrillos mentolados convencionales que desee si está en el grupo 2. Sin embargo, no tendrá libre acceso a los cigarrillos mentolados convencionales ni al producto THS 2.2 Menthol. El personal del estudio distribuirá los cigarrillos mentolados convencionales y las ramas de tabaco del producto THS 2.2 Menthol cuando usted lo solicite, uno a la vez. No está permitido fumar durante la realización de los procedimientos del estudio. El día 6, no podrá fumar ni usar el producto THS 2.2 Menthol antes de que se hayan realizado todos los análisis de laboratorio y todas las pruebas para evaluar la función pulmonar completa. En este estudio no se permite fumar fuera del edificio, por lo tanto, se le pedirá que fume sus cigarrillos mentolados convencionales o que use el producto THS 2.2 Menthol en una cabina para fumar dentro del edificio. La cabina está construida en vidrio y tiene

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espacio para 8 personas a la vez. La cabina utiliza filtros para contener el humo y evitar que salga de allí. Un miembro del personal le explicará cómo usar las cabinas y cómo apagar sus cigarrillos mentolados convencionales o desechar las ramas de tabaco del THS 2.2 Menthol cuando haya terminado de usarlas o de fumar.

Si es asignado al grupo 3, se requiere abstinencia completa de fumar durante todo el estudio, desde el día 1 hasta el día 91. Durante el período de internamiento que abarca desde el día 1 hasta el día 6, el personal del centro supervisará cuidadosamente a todos los participantes de la investigación del grupo 3 para detectar posibles signos y síntomas de la abstinencia de nicotina. Durante este período, no puede usar ningún medicamento para ayudar a la abstinencia de fumar ni usar ningún producto que contenga tabaco/nicotina. Se le brindará ayuda psicológica durante el período de abstinencia de fumar.

Al final del período de internamiento cuando usted sea dado de alta del centro el día 6, se le indicará que continúe con el producto/régimen al cual fue asignado en un contexto ambulatorio durante 86 días; esto es, continuar usando el producto THS 2.2 Menthol, si fue asignado al grupo 1, y continuar fumando los cigarrillos mentolados convencionales, si fue asignado al grupo 2; o bien, abstenerse de fumar, si fue asignado al grupo 3. Tendrá que registrar todos los días en un diario electrónico cualquier uso del producto THS 2.2 Menthol, cigarrillos convencionales (mentolados o no mentolados), terapia de reemplazo de la nicotina, por ejemplo, goma de mascar de nicotina u otros productos que contengan nicotina/tabaco. Si durante el período ambulatorio usa cualquier otro producto que contenga nicotina/tabaco distinto del producto/régimen asignado, no se le pedirá que deje de participar en el estudio.

Durante el período ambulatorio, no habrá restricciones con respecto a fumar/al uso del producto, excepto durante las tres visitas al centro (visitas de los días 30, 60 y 90), cuando se permitirá el uso del producto desde el ingreso por la mañana antes de las 8:30 a. m. hasta las 11:00 p. m. de los días 30, 60 y 90. Los días 31 y 61, se permitirá el uso del producto desde las 6:30 a. m. en adelante. El día 91, se permitirá el uso del producto después de que se hayan realizado algunas evaluaciones (por ejemplo, la Escala Minnesota de abstinencia de la nicotina [*Minnesota Nicotine Withdrawal Scale*] y cuestionarios sobre la tos, evaluaciones de la función pulmonar completa) hasta el momento del alta del día 91. Si fue asignado al grupo de cigarrillos mentolados convencionales o el grupo de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol.

Si fue asignado al grupo del producto THS 2.2 Menthol, el personal del centro le dará instrucciones sobre cómo desechar las ramas de tabaco del producto THS Menthol.

Si es asignado al grupo 1 (grupo del producto THS 2.2 Menthol), durante el período ambulatorio tendrá que visitar el centro aproximadamente cada 2 semanas para que se le suministren nuevos paquetes de ramas de tabaco del producto THS 2.2 Menthol. Durante esta visita no se realizará ninguna otra evaluación. Cuando venga a la clínica para las visitas de los días 30, 60 y 90, deberá devolver al centro los paquetes vacíos, sin usar y abiertos de las ramas de tabaco del producto THS 2.2 Menthol sin usar, así



como las piezas del producto THS 2.2 Menthol (es decir, las ramas de tabaco del THS, la boquilla, el cargador y los accesorios del THS).

Si en cualquier momento durante el estudio desea dejar de fumar, el personal del estudio le ayudará con esta decisión y lo referirá a los servicios médicos. Permanecerá en el estudio y completará las visitas y los procedimientos restantes. Sin embargo, puede decidir retirarse del estudio en cualquier momento.

SELECCIÓN

Acudirá a la clínica para una visita de selección en la que se determinará si usted es elegible para participar en este estudio. La visita de selección tendrá lugar como máximo 28 días antes de la admisión en el centro. Se espera que llegue al centro de investigación habiendo ayunado durante al menos 10 horas, que se requiere para determinados análisis de sangre. Antes de que se realicen las pruebas y los procedimientos relacionados con el estudio, se le pedirá que lea y firme este documento de consentimiento. Para determinar si reúne los requisitos para participar en este estudio, se llevarán a cabo las pruebas y los procedimientos siguientes:

- Se le asesorará sobre el riesgo de fumar (entrevista breve de conformidad con las recomendaciones del Servicio de Salud Pública [*Public Health Service*] de los Estados Unidos), y se le brindará asesoramiento para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se reunirá información demográfica sobre usted (edad, sexo, raza, grupo étnico).
- Se le harán preguntas sobre sus antecedentes médicos y sus condiciones clínicas actuales.
- Se le harán preguntas sobre cualquier medicamento que haya estado usando en el pasado y cualquier medicamento que use actualmente. Se le indicará qué medicamentos podrá usar mientras esté en el estudio.
- Se le preguntará cómo se siente.
- Se le harán preguntas acerca de sus antecedentes de tabaquismo.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o antes (para ello, responderá el cuestionario de Prochaska "Etapa de cambio" [*Stage of Change*]).
- Se le preguntará si está preparado para cumplir con los procedimientos descritos en el protocolo del estudio (por ejemplo, si está preparado para abstenerse de fumar durante un máximo de 91 días).
- Se le preguntará qué marca de cigarrillos mentolados normales fuma.
- Se le realizará una exploración física, se medirán los signos vitales (pulso, presión arterial y frecuencia respiratoria estando previamente en posición de decúbito supino durante al menos 5 minutos) y se medirá la estatura y el peso para calcular el índice de masa corporal (IMC).
- Se le realizará un ECG (electrocardiograma, un trazado indoloro del ritmo cardíaco). Un ECG muestra el patrón de los latidos del corazón. Es posible que a los varones se les deba afeitar el vello del pecho antes de los ECG para que los parches se adhieran a la piel. Las mujeres no podrán usar sostén.
- Se obtendrán muestras de sangre y de orina para realizar análisis de laboratorio clínico, después de un período de ayuno de 10 horas.

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- A las mujeres también se les realizará una prueba de embarazo en orina.
- Se realizarán pruebas para la detección de VIH (SIDA) y hepatitis (de una muestra de sangre), drogas ilegales (de una muestra de orina), cotinina (de una muestra de orina) y alcohol (de una muestra de sangre o de una prueba respiratoria).
- Durante esta visita, el personal del estudio llevará a cabo una demostración del producto THS 2.2 Menthol.
- Se realizará una radiografía del pecho si no se ha realizado una dentro de los 6 meses anteriores. La radiografía se llevará a cabo en una unidad de radiología (rayos X). La radiografía del pecho consta de dos imágenes radiográficas que se toman en ángulos diferentes.
- Se le pedirá que sopla dentro de una máquina llamada espirómetro. Esto se realizará antes y después de inhalar un broncodilatador de acción rápida (medicamento para "abrir" los bronquios). Esta máquina medirá qué tan bien funcionan los pulmones. Esta prueba se realizará al menos una hora después de fumar.
- Se le pedirá que complete un cuestionario específico sobre la dependencia de la nicotina (Prueba de Fagerstrom de dependencia de nicotina [*Fagerstrom Test for Nicotine Dependence*]).
- Se le entregarán dos formularios de consentimiento informado adicionales para subestudios opcionales. Su participación en el estudio principal no depende de su decisión de firmar o no estos formularios de consentimiento informado.

El virus de inmunodeficiencia humana (VIH) es el virus que puede causar el síndrome de inmunodeficiencia adquirida (SIDA). Para poder reunir los requisitos para participar en este estudio, primero debe obtener un resultado negativo en la prueba de anticuerpos contra el VIH. Los anticuerpos son sustancias que produce el sistema inmunitario del cuerpo para combatir infecciones. Un análisis de sangre puede demostrar si usted ha estado expuesto o está infectado con el VIH. La decisión de aceptar realizarse la prueba de VIH es voluntaria y solamente usted puede tomarla. Sin embargo, si elige no realizarse la prueba de VIH, no podrá participar en este estudio. La prueba de anticuerpos contra el VIH se realizará de forma confidencial. Un resultado VIH positivo no significa que usted tenga VIH o SIDA, así como una prueba con resultado negativo no significa que usted no esté infectado porque puede tardar hasta tres meses que la prueba indique la infección. Los resultados positivos de las pruebas de hepatitis y VIH deben informarse a un organismo de salud local. Esta es la obligación legal de los profesionales de la salud en este estado.

Si no reúne los requisitos para participar en el estudio según los resultados de otros procedimientos de selección, o si usted no completa la visita de selección, es posible que estas pruebas de VIH no se realicen.

Se le comunicará que puede continuar fumando su marca preferida de cigarrillos mentolados convencionales.

Se le permitirá participar en el estudio a discreción del médico del estudio si los

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resultados de los análisis de laboratorio de la selección del estudio y de otras evaluaciones realizadas tanto en la selección como el día de la admisión (día -2) son satisfactorios. Es posible que sea necesario repetir los procedimientos de selección para que pueda ingresar en este estudio. Se le comunicarán las restricciones del estudio y cuándo debe regresar a la unidad de investigación para comenzar el estudio.

Es posible que sea necesario repetir algunos procedimientos de selección en el ingreso para confirmar la elegibilidad. Estas pruebas pueden mostrar una modificación desde la selección que indique un cambio en su salud o bienestar físico que quizá haga que usted no sea elegible en el momento del ingreso.

Si después de completar los procedimientos de selección usted reúne los requisitos para el estudio, deberá comprar sus propios cigarrillos mentolados convencionales de la marca que prefiera antes de la admisión. El día -2, deberá entregarle al personal del estudio la cantidad de paquetes que considere que podría fumar durante 9 días más 4 paquetes adicionales. El patrocinador no proporcionará los cigarrillos mentolados convencionales. Los paquetes sin usar o usados parcialmente se le devolverán cuando sea dado de alta del centro.

PROCEDIMIENTOS DEL ESTUDIO

Periódicamente durante el estudio, se medirán los signos vitales (presión arterial, pulso) y se realizarán ECG. También se le harán preguntas para saber cómo se siente y si ha usado algún medicamento. Además, las muestras de sangre y/o de orina obtenidas en este estudio pueden usarse para realizar análisis de laboratorio clínico de rutina, análisis del medicamento del estudio, constituyentes del humo seleccionados, biomarcadores, marcadores de riesgo, niveles de nicotina y monóxido de carbono. También se le pedirá que complete varios cuestionarios sobre los cigarrillos, el hábito de fumar, la preferencia de fumar, su percepción de los riesgos asociados con el uso del producto THS 2.2 Menthol y la abstinencia de fumar. Consulte a continuación la lista de evaluaciones que deberá realizar cada día.

En función del diseño del estudio, es posible que sea seleccionado como suplente para este estudio. En este caso, puede seguir los procedimientos de las secciones Admisión y Visita inicial (día -1 y día 0), pero no será asignado a ningún grupo del estudio ni participará en el resto del estudio.

Día -2 (admisión/ingreso)

El día -2 concurrirá al centro de investigación para comenzar su internamiento en el centro de investigación.

Si es elegible:

- Se le realizará una exploración física, y se medirá su peso y cintura. Se calculará el índice de masa corporal.
- Se obtendrán muestras de orina para realizar análisis de laboratorio (pruebas para



detectar el uso de drogas ilegales y una prueba de embarazo en orina para las mujeres).

- Se le preguntará cómo se siente.
- Se le harán preguntas sobre cualquier medicamento que esté usando actualmente y sus condiciones clínicas actuales.
- Recibirá información sobre el riesgo de fumar/asesoramiento para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se le preguntará acerca de sus antecedentes de tabaquismo.
- Se realizará una prueba de alcohol (en una muestra de orina o una prueba respiratoria).
- Se le preguntará si está preparado para cumplir con los procedimientos descritos en el protocolo del estudio (por ejemplo, si está preparado para abstenerse de fumar durante un máximo de 91 días).
- Se realizará una prueba de medición de monóxido de carbono en el aliento (medición de la cantidad de monóxido de carbono en el aliento).
- Se medirán los signos vitales (presión arterial, frecuencia del pulso, frecuencia respiratoria).
- Se identificará la marca de cigarrillo mentolado convencional que fuma actualmente (deberá entregarle al personal del centro su propio suministro de cigarrillos mentolados convencionales para el período de internamiento. Tomarán una fotografía del paquete).
- Antes de la prueba del producto THS 2.2 Menthol, se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o antes (para ello, responderá el cuestionario de Prochaska "Etapa de cambio").
- Realizará una prueba del producto THS 2.2 Menthol (solamente después de que se confirme un resultado negativo en la prueba de embarazo en las mujeres). Como último procedimiento de los criterios de elegibilidad, probará el producto THS 2.2 Menthol (usando como máximo 3 ramas de tabaco mentolado). A continuación, se le preguntará si está listo para usar el producto THS 2.2 Menthol durante el tiempo que dure el estudio, si fue asignado de forma aleatoria al grupo 1.
- Si cumple con todos los criterios de elegibilidad, será inscrito en el estudio.
- Después de confirmar su inscripción en el estudio, se le preguntará a qué producto preferiría ser asignado de forma aleatoria, si pudiera elegir el grupo del estudio (preguntas de preferencia de producto). Sin embargo, tenga en cuenta que, en realidad, el grupo del estudio en el que ingrese se decidirá de forma aleatoria y usted no puede elegirlo. Si prefiere ser asignado de forma aleatoria al grupo SA, se le pedirá nuevamente que responda el cuestionario de Prochaska "Etapa de cambio". Según su respuesta, es posible que sea retirado del estudio.

Continuará fumando sus propios cigarrillos mentolados convencionales hasta las 11:00 p. m.

Visita inicial, día -1

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- Desde las 10:00 a. m. hasta las 2:00 p. m., usted orinará en recipientes desechables que luego le entregará al personal del centro. El personal del centro le proporcionará información detallada sobre el método de obtención de orina. La orina obtenida se usará para analizar biomarcadores de exposición y marcadores de riesgo.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizarán pruebas de determinación de monóxido de carbono en el aliento cuatro veces por día; la primera prueba se llevará a cabo 15 minutos antes de la primera vez que fume y las otras pruebas tendrán lugar entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m.
- Se medirán los signos vitales (presión arterial, frecuencia cardíaca y frecuencia respiratoria).
- Cuestionario de impulsos de fumar (deseo de fumar) (*Questionnaire of Smoking Urges*): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos (*Modified Cigarette Evaluation Questionnaire*): se le pedirá que complete un cuestionario para evaluar el producto THS 2.2 Menthol y los cigarrillos mentolados convencionales.
- Se le pedirá que complete dos cuestionarios para evaluar su conducta actual y anterior con respecto al hábito de fumar (Cuestionario de factores de riesgo conductuales [*Behavioral Risk Factor Questionnaire*] y Cuestionario sobre el hábito de fumar [*Smoking Questionnaire*]) y datos complementarios sobre la conducta relacionada con el hábito de fumar.
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (una medición de los niveles de monóxido de carbono en la sangre), entre las 8:00 y las 9:30 p. m.
- Se deberán juntar todas las colillas de cigarrillos mentolados convencionales que haya fumado para llevar un control.

Visita inicial, día 0

Lo despertarán temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio.

- Comienzo de la obtención de orina de 24 horas del día 0 (cada vez que orine deberá hacerlo en recipientes desechables que luego le entregará al personal del centro). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará una prueba de determinación de monóxido de carbono en el aliento (cuatro veces por día; la primera prueba se llevará a cabo 15 minutos antes de la primera vez que fume y las otras pruebas tendrán lugar entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m.).
- Se obtendrán muestras de sangre para el día 0 de la siguiente manera:

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- Una muestra para hematología, bioquímica clínica y marcadores de riesgo: se obtendrá después de al menos 10 horas de ayuno.
- Una muestra de sangre para el almacenamiento en banco de material biológico a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (si da su consentimiento para esta muestra) (debe realizarse después de al menos 10 horas de ayuno).
- Una muestra para almacenamiento en banco de material biológico para realizar análisis adicionales de investigación transcriptómica (si dio su consentimiento para una muestra para pruebas genéticas) (se debe realizar después de al menos 10 horas de ayuno).
- Una muestra para medir los oxisteroles ("colesterol") en la sangre (se debe realizar después de al menos 10 horas de ayuno).
- Una muestra para medir la carboxihemoglobina (una medida de la concentración de monóxido de carbono en la sangre) (antes de las pruebas para evaluar la función pulmonar completa)
- Una muestra para medir la actividad de la enzima CYP2A6, una entidad biológica involucrada en el metabolismo de la nicotina en la sangre (se debe realizar antes de fumar).
- Una muestra para medir la actividad de la enzima CYP1A2 (que interviene en el metabolismo de la cafeína), entre las 4:00 y las 5:30 p. m., 6 horas después de haber ingerido un comprimido de cafeína.
- Una muestra para medir la carboxihemoglobina (una medición de los niveles de monóxido de carbono en la sangre), entre las 8:00 y las 9:30 p. m.
- Una muestra para medir los niveles de nicotina y cotinina en la sangre, entre las 8:00 y las 9:30 p. m.
- Tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 240 ml de agua (para medir la enzima CYP1A2), entre las 10:00 y las 11:30 a. m.
- Se realizará una prueba de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes de fumar.
- Se obtendrá una muestra de orina para realizar análisis de seguridad.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Se realizará una topografía del fumador (un procedimiento indoloro para evaluar la conducta con respecto al hábito de fumar) solamente si se le proporciona el dispositivo HST SODIM® (un dispositivo que mide la forma individual de fumar de una persona). Tenga en cuenta que si le entregan el dispositivo HST SODIM®, debe usarlo todas las veces que fume el día 0.
- Cuestionario sobre topografía del fumador: si se le entrega el dispositivo HST SODIM® también se le pedirá que complete un cuestionario para evaluar el uso del HST en rituales relacionados con el hábito de fumar entre las 8:00 y las 11:00 p. m.

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- Evaluación de la tos (se le pedirá que complete un cuestionario en el que se evalúa la tos) y la Escala Minnesota de abstinencia de la nicotina (se le pedirá que complete un cuestionario para evaluar los signos y síntomas de la abstinencia). Los cuestionarios se deben completar antes de fumar, pero no más tarde de las 10:00 a. m.
- Se le pedirá que complete un cuestionario para evaluar el producto (Cuestionario modificado de evaluación de cigarrillos) y un cuestionario para evaluar su deseo de fumar (Cuestionario de impulsos de fumar), entre las 8:00 y las 11:00 p. m.
- Obtención de células epiteliales nasales (obteniones de células de la nariz) y de una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalles si firma el formulario de consentimiento informado correspondiente a cada uno.
- Se recogerán todas las colillas de los cigarrillos mentolados convencionales que haya fumado para llevar un control.

Días 1 a 5 del período de exposición

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio

- Antes de las 6:30 a. m. del día 1, se le comunicará a qué grupo del estudio ha sido asignado de forma aleatoria.
- Recibirá asistencia para abstenerse de fumar, si fuese necesario (solamente el grupo de abstinencia de fumar).
- Se realizará la obtención de orina de 24 horas desde la mañana del día 1 hasta la mañana del día 6 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del centro). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- El día 1 finaliza la obtención de orina de 24 horas que había comenzado el día 0. La orina obtenida durante las 24 horas se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo, además se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para almacenarlas a largo plazo en un banco de material biológico y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- La orina obtenida durante las 24 horas de los días 2, 3, 4 y 5 se usará para analizar los biomarcadores de exposición y la creatinina.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrán muestras de sangre para realizar lo siguiente:
 1. Medición de la carboxihemoglobina: días 1 a 4, una muestra de sangre al anochecer, entre las 8:00 y las 9:30 p. m., cada día. Día 5, una muestra de sangre dentro de los 15 minutos anteriores al primer uso del producto del día, entre las 8:00 y las 9:30 a. m., para los sujetos del grupo de abstinencia de fumar, seguida de tres muestras de sangre adicionales entre las 12:00 y la

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1:30 p. m., las 4:00 y las 5:30 p. m., y las 8:00 y las 9:30 p. m., para todos los sujetos.

2. Medición de la nicotina/cotina: días 1 a 4, una muestra de sangre al anochecer, entre las 8:00 y las 9:30 p. m., cada día. El día 5, solamente para los grupos del producto THS 2.2 Menthol y de cigarrillos mentolados convencionales, una muestra de sangre dentro de los 15 minutos anteriores al primer uso del producto de ese día seguida de ocho muestras a intervalos de 2 horas. Para los sujetos asignados de forma aleatoria al grupo de abstinencia de fumar, el día 5 se obtendrá una muestra de sangre por la noche, entre las 8:00 y las 9:30 p. m.
- Solamente el día 5, se obtendrá una muestra de sangre para medir la actividad de la enzima CYP1A2 (que interviene en el metabolismo de la cafeína): la muestra se obtendrá entre las 4:00 y las 5:30 p. m., 6 horas después de haber tomado un comprimido de cafeína.
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento, cuatro veces al día: la primera prueba se realizará 15 minutos antes del primer cigarrillo o uso del producto, entre las 8:00 y las 9:30 de la mañana, para los sujetos del grupo de abstinencia de fumar; las otras pruebas se llevarán a cabo aproximadamente entre las 12:00 y la 1:30 p. m., las 4:00 y las 5:30 p. m. y las 8:00 y las 9:30 p. m., para todos los sujetos (días 1 a 5).
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: días 1 a 5).
- Evaluación de la tos (se le pedirá que complete un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (se le pedirá que complete un cuestionario para evaluar los signos y síntomas de la abstinencia) (debe realizarse antes de fumar, no más tarde de las 10:00 a. m., los días 1 a 5).
- Se le pedirá que complete un cuestionario para evaluar el producto (Cuestionario modificado de evaluación de cigarrillos) y un cuestionario para evaluar su deseo de fumar (Cuestionario de impulsos de fumar), entre las 8:00 y las 11:00 p. m. de los días 1 a 5.
- Solamente el día 4, se le pedirá que complete un cuestionario sobre su estado socioeconómico. Se le hará una serie de preguntas relacionadas con su educación, estado ocupacional, cantidad de personas que viven con usted e ingreso anual de su casa. Puede responder todas las preguntas que desee.
- Solamente el día 4, se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales y se le proporcionó el dispositivo HST SODIM®).
- Solamente el día 5, se le pedirá que complete dos cuestionarios para evaluar su conducta actual y anterior con respecto al hábito de fumar (Cuestionario de factores de riesgo conductuales y Cuestionario sobre el hábito de fumar) y datos complementarios con respecto a la conducta relacionada con el hábito de fumar.
- Solamente el día 5, tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 240 ml de agua (para medir la enzima CYP1A2), entre las 10:00 y las 11:30 a. m.

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- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que si se le entrega el dispositivo HST SODIM®, y está en el grupo del producto THS 2.2 Menthol y de cigarrillos mentolados convencionales, debe utilizarlo para todos los usos de producto (días 1 a 4).

Fumar los cigarrillos mentolados convencionales o usar el producto THS 2.2 Menthol está permitido de 6:30 a. m. a 11:00 p. m., pero no durante los procedimientos del estudio. Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas del producto THS 2.2 Menthol y las colillas de los cigarrillos mentolados convencionales (días 1 a 5). En el grupo del producto THS 2.2 Menthol, se le pedirá que recoja todos los restos de tabaco usados en los frascos exclusivos que le entregará el personal.

Día 6 (alta)

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio

- Recibirá asistencia para abstenerse de fumar, si fuese necesario (solamente el grupo 3).
- Se obtendrán muestras de sangre (que incluyen muestras para medir un perfil de nicotina: se extraerán dos muestras de sangre, la primera tendrá lugar 20 horas después de la hora de inicio del primer uso del producto, el día 5, y la segunda será 24 horas después del inicio del primer uso del producto, el día 5. En el caso del grupo de abstinencia de fumar, se extraerá una sola muestra de sangre entre las 8:00 y las 9:30 a. m.).
- El día 6 finaliza la obtención de orina de 24 horas que comenzó el día 5. Esta muestra se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo; además, se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para el almacenamiento en banco de material biológico a largo plazo y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- Se obtendrán muestras de sangre y de orina para realizar análisis de laboratorio (hematología, bioquímica clínica, después de un período de al menos 10 horas de ayuno), un análisis de orina general y una prueba de embarazo en orina para todas las mujeres.
- Se obtendrán muestras de sangre para realizar análisis de marcadores de riesgo (después de al menos 10 horas de ayuno).
- Se obtendrán muestras de sangre para almacenamiento a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.

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- Se obtendrá una muestra de sangre para almacenamiento a largo plazo para realizar análisis adicionales de transcriptómica (después de un período de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Se obtendrá una muestra de sangre para medir los oxisteroles (después de un período de al menos 10 horas de ayuno).
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (antes de la prueba para evaluar la función pulmonar completa).
- Se obtendrá una muestra de sangre para medir la actividad de la enzima CYP2A6 (se debe realizar antes de fumar).
- Se realizará una exploración física que incluye la medición del peso y el cálculo del índice de masa corporal.
- Completará un cuestionario de Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia) (se debe realizar antes del uso del producto, pero no más tarde de las 10:00 a. m.).
- Se realizarán pruebas de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espirómetro). Todas las evaluaciones se debe realizar antes del uso del producto.
- Se realizará una prueba de determinación de monóxido de carbono en el aliento.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria).
- Se realizará un electrocardiograma (un trazado indoloro del ritmo y la frecuencia cardíaca).
- Se le asesorará sobre el riesgo de fumar y sobre la importancia de dejar de fumar, y se le proporcionará información sobre el producto THS 2.2 Menthol.
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrán células epiteliales nasales (obteniones de células de la nariz) y una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalle si firma el formulario de consentimiento informado correspondiente a cada uno.
- Será dado de alta del centro.

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas del producto THS 2.2 Menthol y las colillas de los cigarrillos mentolados convencionales. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Antes ser dado de alta del centro, se le entregará un diario electrónico que usará para registrar cualquier uso de las ramas de tabaco del producto THS 2.2 Menthol, los

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cigarrillos convencionales (mentolados y no mentolados), los productos de terapia de sustitución de la nicotina o el uso de otros productos que contengan nicotina/tabaco. Todos los participantes, incluidos los del grupo 3, deben completar este diario todos los días desde el momento del alta el día 6 hasta el momento del alta el día 91. Recibirá capacitación para usar este diario electrónico.

Después del alta el día 6, se le indicará que continúe utilizando el producto/régimen que se le asignó en su casa durante 86 días. Si se lo asignó al grupo SA, es posible que se le proporcione terapia de sustitución de la nicotina (no se permitirá el uso de ningún otro producto medicinal para dejar de fumar) si el investigador lo considera necesario o si usted lo solicita.

Visita del día 30 (desde el ingreso antes de las 8:30 a. m. del día 30 hasta la salida el día 31) y **visita del día 60** (desde el ingreso antes de las 8:30 a. m. hasta la salida el día 61)

Se permitirá fumar o usar el producto en el centro desde el ingreso hasta aproximadamente las 11:00 p. m. de los días 30 y 60 y desde las 6:30 a. m. de los días 31 y 61. No hay restricciones con respecto a fumar/al uso del producto antes del ingreso al centro. Si fue asignado al grupo de cigarrillos mentolados convencionales o al de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol. Durante las visitas de los días 30 y 60, se le pedirá que continúe completando el diario electrónico todos los días.

Se le pedirá que traiga suficiente suministro del producto que ha estado usando para cubrir su estadía durante el internamiento. Se le proporcionarán ramas de tabaco del producto THS 2.2 Menthol durante su estadía en la clínica. Si se lo asigna al grupo del producto THS 2.2, tendrá que traer todos los paquetes vacíos y las ramas de tabaco de producto THS 2.2 sin usar. También deberá traer el dispositivo THS 2.2 (con todas las piezas: las boquillas, el cargador, la herramienta de limpieza, la fuente de energía principal y el cable USB) y el diario electrónico.

Durante los días 30 y 60, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará la obtención de orina de 24 horas desde la mañana de los días 30 y 60 hasta la mañana de los días 31 y 61 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del estudio). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Prueba de embarazo en orina (para las mujeres).
- Obtención de una muestra de sangre para medir la carboxihemoglobina.
- Obtención de una muestra de sangre para medir la nicotina y la cotinina en la

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sangre.

- Exploración física que incluye la medición del peso y el cálculo del índice de masa corporal.
- Se le realizará un ECG (electrocardiograma, un trazado indoloro del ritmo cardíaco).
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Cuestionario de impulsos de fumar (deseo de fumar): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos: se le pedirá que complete un cuestionario para evaluar el producto.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o menos (respondiendo el cuestionario de Prochaska "Etapa de cambio").
- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que el dispositivo HST SODIM® debe utilizarse para todo los usos de producto de los grupos de THS 2.2 Menthol y cigarrillos mentolados convencionales durante un período de 4 horas cada día y solamente con el producto al cual usted ha sido asignado.
- Se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®).

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Días 31 y 61

Durante estos días, usted puede comenzar a fumar/usar el producto desde las 6:30 a. m.

Durante los días 31 y 61, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo 3).
- Preguntas sobre cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Obtención de muestras de sangre para realizar análisis de laboratorio (hematología, bioquímica clínica) y análisis de marcadores de riesgo después de un período de al menos 10 horas de ayuno.
- Finalización de la obtención de orina de 24 horas desde el día 30 o el día 60. La orina obtenida durante 24 horas se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo.

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- Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia).
- Análisis de orina de seguridad.
- Recibirá asesoramiento sobre el riesgo de fumar/para dejar de fumar e información sobre el producto THS 2.2 Menthol.

Visita del día 90 (desde el ingreso antes de las 8:30 a. m. del día 90 hasta el alta el día 91)

Se le pedirá que traiga suficientes ramas de tabaco, de las que ha estado usando, para su estadía en la clínica. Se reabastecerán las ramas de tabaco del producto THS 2.2 durante su estadía en la clínica.

Si es asignado al grupo del producto THS 2.2, para esta visita tendrá que traer todos los paquetes vacíos o sin usar y las ramas de tabaco de producto THS 2.2 sin usar. También deberá traer el dispositivo de calentamiento de tabaco (con todas las piezas: las boquillas, el cargador, la herramienta de limpieza, la fuente de energía principal y el cable USB) y el diario electrónico. Dejará todos estos suministros en el centro el día 91, cuando sea dado de alta.

Se permitirá fumar o usar el producto en el centro desde el ingreso hasta aproximadamente las 11:00 p. m. y el día 91 solamente después de que se haya realizado la medición de la actividad de la enzima CYP2A6 y la espirometría. No hay restricciones para fumar/usar el producto antes del ingreso al centro. Si fue asignado al grupo de cigarrillos mentolados convencionales o al de abstinencia de fumar, no podrá usar el producto THS 2.2 Menthol.

Durante la visita del día 90, se le pedirá que continúe completando el diario electrónico todos los días.

Día 90

Durante el día 90, se realizarán las siguientes actividades:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).
- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se realizará una topografía del fumador (para evaluar su conducta relacionada con el hábito de fumar) si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®. Tenga en cuenta que el dispositivo HST SODIM® debe usarse para todo los usos de producto de los grupos de THS 2.2 Menthol y cigarrillos mentolados convencionales durante un período de 4 horas cada día y solamente con el

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producto al cual usted ha sido asignado.

- Se le pedirá que complete el cuestionario del dispositivo HST (si está en el grupo del producto THS 2.2 Menthol o de cigarrillos mentolados convencionales, y se le proporcionó el dispositivo HST SODIM®).
- Se realizará la obtención de orina de 24 horas desde la mañana del día 90 hasta la mañana del día 91 (cada vez que orine, lo hará en recipientes desechables que luego entregará al personal del estudio). El personal del centro le proporcionará información detallada sobre el método de obtención de orina.
- Tomará un comprimido de aproximadamente 200 mg de cafeína con alrededor de 240 ml de agua.
- Se le realizará una prueba de determinación de monóxido de carbono en el aliento.
- Obtención de una muestra de sangre para medir la carboxihemoglobina.
- Obtención de una muestra de sangre para medir la nicotina y la cotinina en la sangre.
- Obtención de una muestra de sangre para medir la actividad de la enzima CYP1A2, que se realizará 6 horas después de que haya tomado el comprimido de cafeína.
- Obtención de células epiteliales nasales (obteniones de células de la nariz) y de una muestra bucal (obtención de células de la boca), solamente si ha firmado el consentimiento informado opcional para estos procedimientos. Estos procedimientos se le explicarán con más detalle si firma el formulario de consentimiento informado correspondiente a cada uno.
- Cuestionario de impulsos de fumar (deseo de fumar): se le pedirá que complete un cuestionario para indicar su antojo.
- Cuestionario modificado de evaluación de cigarrillos: se le pedirá que complete un cuestionario para evaluar el producto.
- Se le preguntará si está pensando seriamente en dejar de fumar en los próximos 6 meses o menos (respondiendo el cuestionario de Prochaska "Etapa de cambio").
- Se le pedirá que complete un cuestionario específico sobre la dependencia de la nicotina (Prueba de Fagerstrom de dependencia de nicotina).

Tenga en cuenta que se recogerán todas las ramas de tabaco mentolado usadas. En el grupo del producto THS 2.2, se les pedirá a los sujetos que recojan todos los restos de tabaco usados en los frascos exclusivos que les entregará el personal.

Día 91

Es posible que lo despierten temprano a la mañana para que haya tiempo suficiente para llevar a cabo todos los procedimientos requeridos del estudio.

Durante este día, se realizarán los siguientes procedimientos:

- Ayuda para abstenerse de fumar, si fuese necesario (solamente para el grupo de abstinencia de fumar).

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- Se le preguntará cómo se siente y sobre cualquier medicamento que esté usando actualmente.
- Se obtendrá una muestra de sangre para medir la actividad de la enzima CYP2A6 en la sangre. Esta muestra de sangre se obtendrá antes de que fume o use el producto THS 2.2 Menthol.
- Se obtendrá una muestra de sangre para medir la carboxihemoglobina (antes de la prueba de la función pulmonar completa).
- Se realizarán pruebas de la función pulmonar completa (espirometría con broncodilatador, y otras dos técnicas usando un espiómetro). Todas las evaluaciones se debe realizar antes del uso del producto.
- Obtención de muestras de sangre para realizar análisis de laboratorio (hematología, bioquímica clínica) y marcadores de riesgo, después de un periodo de al menos 10 horas de ayuno.
- Una muestra de sangre para medir los oxiesteroles, después de un periodo de al menos 10 horas de ayuno.
- Un análisis de seguridad en orina, y una prueba de embarazo en orina para todas las mujeres.
- Exploración física que incluye la medición del peso, el perímetro de la cintura y el cálculo del índice de masa corporal.
- Se medirán los signos vitales (presión arterial, frecuencia del pulso y frecuencia respiratoria: en posición de decúbito supino durante al menos 5 minutos antes de la medición).
- Se le realizará un electrocardiograma, un trazado indoloro del ritmo cardíaco.
- Obtención de muestras de sangre para el almacenamiento a largo plazo de suero y plasma para realizar análisis adicionales de biomarcadores de exposición y marcadores de riesgo (después de un periodo de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Obtención de una muestra de sangre para almacenamiento a largo plazo para realizar análisis adicionales de transcriptómica (después de un periodo de al menos 10 horas de ayuno), solamente si usted ha firmado el consentimiento informado opcional para estos procedimientos.
- Finalización de la obtención de orina de 24 horas que comenzó el día 90. Esta muestra se usará para analizar los biomarcadores de exposición, la creatinina y los marcadores de riesgo; además, se realizará una prueba de mutagenicidad. Las muestras de orina se conservarán para el almacenamiento en banco de material biológico a largo plazo y para realizar análisis adicionales, siempre y cuando se haya dado el consentimiento para este procedimiento.
- Comienzo de la obtención de orina de 4 horas el día 91 (a partir de las 10:00 a. m. y durante un periodo de 4 horas, cada vez que orine, lo hará en recipientes desechables que luego le entregará al personal del centro). La orina obtenida se usará para analizar los biomarcadores de exposición y los marcadores de riesgo.

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- Recibirá asesoramiento sobre el riesgo de fumar/para dejar de fumar e información sobre el producto THS 2.2 Menthol.
- Se le pedirá que complete una Evaluación de la tos (un cuestionario para evaluar la tos) y la Escala Minnesota de abstinencia de la nicotina (un cuestionario para evaluar los signos y síntomas de la abstinencia).
- Antes de abandonar el centro deberá entregarle al personal del centro el dispositivo THS 2.2 Menthol, las ramas de tabaco del producto THS 2.2 sin usar (si está en el grupo 1) y el diario electrónico.

Período de seguimiento de seguridad:

Habrà un período de seguimiento de seguridad durante 28 días después de la última visita del estudio planificada (alta del día 91 o finalización anticipada). Si se retira del estudio de forma anticipada, ingresará en el período de seguimiento el día que se retire.

Si participó en la prueba del producto del día -2, pero no fue inscrito en el estudio, aun así ingresará en el período de seguimiento de 28 días.

Durante este período de seguimiento de seguridad, debe comunicarle al centro cualquier problema médico nuevo que experimente. El personal del centro también se comunicará con usted para realizar un seguimiento de cualquier problema médico que usted comunique durante el estudio o durante el período de seguimiento que no se haya resuelto después de haber sido dado de alta del centro.

Procedimientos de retirada

Si usted se retira de forma anticipada del estudio por cualquier motivo, es posible que se le pida que complete los análisis de laboratorio y los procedimientos descritos anteriormente en la sección Día 6.

No se le permitirá traer su propia comida o bebida al centro de investigación. Las comidas se servirán según los cronogramas predeterminados para este estudio. Si tiene cualquier pregunta relacionada con las comidas, hable con su médico del estudio. Habrá disponible bocadillos ligeros, frutas y verduras crudas sin restricciones en cualquier momento durante el período de internamiento. El consumo de agua también está permitido sin restricciones. Se les proporcionará a los participantes de todos los grupos del estudio un menú estándar y un cronograma de comidas.

Muestras de sangre y orina

Durante todo el estudio, se extraerán aproximadamente 316 ml de sangre (alrededor de 1 taza y ¼). A modo de comparación, una donación estándar de sangre en un centro de obtención de sangre, una vez dentro de cualquier período de 56 días, representa aproximadamente 500 ml (alrededor de 2 tazas) de sangre.

El personal capacitado y cualificado del centro será responsable de la obtención de las muestras de sangre. El volumen total máximo de sangre extraída incluye 40 ml para los

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análisis de seguridad y repetidos, 30 ml para almacenamiento a largo plazo de muestras en un banco de material biológico para realizar análisis adicionales de biomarcadores de exposición en el cuerpo y marcadores de riesgo (solamente si se otorgan los consentimientos adicionales) y 15 ml para el almacenamiento a largo plazo de las muestras en un banco de material biológico para realizar análisis adicionales de transcriptómica (solamente si se otorgan los consentimientos adicionales).

Es posible que se requieran muestras de sangre adicionales si alguno de sus valores de laboratorio fuera anormal. Es posible que sea necesario hacer más de un intento para obtener una muestra de sangre. Pueden obtenerse muestras de sangre adicionales durante el estudio si el médico del estudio lo considera necesario para supervisar su salud. Las muestras de sangre obtenidas se analizarán mediante el uso de métodos validados, a excepción de los oxiesteroides que serán analizados en un laboratorio correctamente equipado. El laboratorio de análisis designado será responsable de conservar las muestras durante este período y de su posterior destrucción. En todo momento durante el estudio, se mantendrá la seguridad de su información personal y su identidad permanecerá anónima.

Las muestras de sangre y de orina para los análisis de laboratorio de seguridad se evaluarán en el centro o en un laboratorio designado, y se conservarán durante aproximadamente 2 meses y luego serán destruidas.

Todas las muestras de sangre y de orina para la medición de biomarcadores de exposición y marcadores de riesgo se analizarán y se conservarán según la documentación relevante del laboratorio.

Las muestras que proporcione solamente se usarán para los objetivos relacionados con el estudio, y no se realizará ningún otro análisis que no sean los análisis relacionados con el estudio que se han descrito en esta hoja de información sin la aprobación suya y del comité de ética.

Todos los datos reunidos se almacenarán durante el tiempo que sea necesario según las leyes, regulaciones y normas vigentes, para garantizar que los datos estén disponibles para las inspecciones del estudio que realicen las autoridades normativas, así como para garantizar la integridad del estudio.

Si bien las investigaciones futuras en las que se usen sus muestras pueden derivar en el desarrollo de nuevos productos, usted no recibirá ninguna compensación por estos productos nuevos. Al aceptar este uso, usted renuncia a todo reclamo de dinero que los investigadores obtengan del uso comercial o de otro tipo de estas muestras.

Responsabilidades del participante de la investigación

Como participante de una investigación, se le pedirá que complete los procedimientos de este estudio, que acuda a la clínica del estudio para hacer todas las visitas programadas, que siga las instrucciones señaladas en este formulario de consentimiento informado y que notifique al médico del estudio si cambia algún dato relacionado con su salud o su disponibilidad para participar en este estudio.

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**Restricciones generales**

- Para evitar la contaminación cruzada de distintos productos, el grupo 1 (THS 2.2 Menthol) y el grupo 2 (cigarrillos mentolados convencionales) deben usar los productos a los que han sido asignado en cabinas para fumar separadas. El grupo 3 (abstinencia de fumar) no podrá estar en la zona de fumadores.
- No debe haber usado medicamentos recetados NI medicamentos de venta libre durante 4 semanas antes del inicio del estudio ni durante todo el estudio, incluido el período de seguimiento de seguridad. Comuníquese al médico del estudio cualquier medicamento (recetado, de venta libre, suplementos a base de hierbas/vitaminas) que esté tomando. Él podrá decirle si está permitido o no que los tome durante el estudio.
- No debe haber participado en un estudio de investigación dentro de los últimos 3 meses.
- No debe haber donado sangre o plasma (por ejemplo, plasmaféresis) dentro de los 3 meses anteriores a la admisión.

Si es asignado al grupo 1, no podrá fumar ningún cigarrillo mentolado convencional ni usar ningún producto que contenga tabaco/nicotina (incluida la terapia de reemplazo de la nicotina) desde el día 1 (6:30 a. m.) hasta el momento del alta el día 6.

Restricciones alimenticias

- Se servirán comidas y bocadillos estandarizados (y controlados en calorías) a intervalos regulares durante su internamiento en la clínica, excepto cuando se requiera ayuno o se indique lo contrario.
- Durante el período de internamiento, no se permitirá el consumo de carne asada o frita, carnes precocidas ahumadas (por ejemplo, atún, jamón, carne de vaca en conserva y carnes), tocino ahumado y salchichas.
- Durante el período de internamiento, no se permitirá el consumo de alcohol, brócoli, coles de Bruselas, coliflor, jugo de pomelo o toronja, y alimentos y bebidas que contengan xantina (café, té, chocolate, cacao, mate, guaraná, etc.).
- No está permitido el consumo de bebidas que contengan quinina (por ejemplo, agua tónica) durante el período de internamiento.
- Un día antes de la visita del día 90, no debe consumir jugo de pomelo o toronja ni productos que contengan pomelo o toronja, ni bebidas que contengan quinina (por ejemplo, agua tónica). No se permite el consumo de bebidas alcohólicas, coles de Bruselas, coliflor, carne asada, alimentos o bebidas que contengan xantinas (por ejemplo, café, té, chocolate, cacao, mate, guaraná) en el centro durante la visita ambulatoria.
- No se le permitirá traer su propia comida o bebida al centro de investigación.
- Las comidas se servirán según los cronogramas predeterminados para este estudio. Si tiene cualquier pregunta relacionada con las comidas, hable con su médico del estudio.
- Habrá disponible bocadillos ligeros, frutas y verduras crudas sin restricciones en cualquier momento durante el período de internamiento.

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- El consumo de agua también está permitido sin restricciones.
- Se les proporcionará a los participantes de todos los grupos del estudio un menú estándar y un cronograma de comidas.

RIESGOS Y MOLESTIAS

Es posible que haya riesgos para usted si participa en este estudio. Como consumidor de tabaco, los riesgos asociados con el uso del tipo de producto con tabaco que consume normalmente seguirán siendo los mismos. En este momento, el uso del producto THS 2.2 Menthol no proporciona ningún riesgo menor de desarrollar enfermedades relacionadas con el tabaco que los cigarrillos de la marca que fuma habitualmente.

Fumar provoca adicción y causa a los fumadores graves enfermedades mortales como cáncer de pulmón, enfermedades pulmonares y cardiovasculares (enfermedad cardíaca), además de otras enfermedades graves. Ningún cigarrillo es seguro. Lo único que se ha demostrado que reduce el riesgo de desarrollar enfermedades relacionadas con fumar en fumadores es dejar de fumar. A pesar de los riesgos atribuibles al tabaquismo, algunos fumadores tienen dificultades para dejar de fumar o deciden seguir fumando.

Fumar tabaco es perjudicial, y los estudios médicos han demostrado que fumar tabaco es una de las causas principales de muchas enfermedades. Si acepta, durante las visitas le proporcionaremos más información sobre los riesgos relacionados con fumar y le asesoraremos para dejar de fumar.

También puede experimentar síntomas de abstinencia y antojos durante todo el estudio, según el grupo al que fue asignado. Es posible que durante este período experimente algunos síntomas conocidos de abstinencia de la nicotina, entre ellos: antojos de tabaco, irritación, ira, problemas de concentración, dolores de cabeza, fatiga, estreñimiento, inquietud, insomnio, mareos y ansiedad.

El uso particular del producto THS 2.2 Menthol puede implicar riesgos para el sujeto (o el embrión o feto, si la participante está embarazada o puede quedar embarazada). Actualmente, estos riesgos son imprevisibles.

Si tiene seguro médico privado, puede que tenga que hacerle saber a los aseguradores que usted tiene intenciones de participar en un proyecto de investigación para que puedan comunicarle si esto afectará su seguro.

Existe la posibilidad de que las distintas pruebas que se llevan a cabo durante el estudio permitan descubrir un problema médico del cual usted no tenía conocimiento previo. Si esto sucede, el médico de la investigación hará los arreglos necesarios para que reciba un tratamiento adecuado y/o, con su permiso, lo derivará a su médico de atención primaria.

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No se le permitirá usar terapia de sustitución de la nicotina ni otros productos de ayuda para dejar de fumar durante su estadía en la clínica.

Tenga en cuenta que todos los médicos que trabajan en el centro de investigación están capacitados y cuentan con certificación en procedimientos de soporte vital avanzado para tratar cualquier emergencia médica. Los enfermeros y otro personal de la clínica también están capacitados en procedimientos de emergencia.

En estudios clínicos anteriores, se han evaluado versiones anteriores del producto THS 2.2 Menthol, que no han demostrado preocupaciones con respecto a la seguridad. Sin embargo, al participar en este estudio, es posible que usted experimente algunos eventos (incluidos, entre otros, dolor de cabeza, dolor causado por la extracción de sangre y mareos). Si sufre alguno de estos efectos secundarios o cualquier otro efecto secundario, debe buscar ayuda médica y comunicarse con el médico o el personal del estudio.

Es posible que haya otros riesgos para usted mientras participa en este estudio. Puede experimentar algunas molestias asociadas con el uso del producto THS 2.2 Menthol que no se han comunicado con anterioridad. Es posible que haya algunos riesgos desconocidos o poco frecuentes e imprevisibles asociados con el uso de este producto del estudio, incluso reacción alérgica o interacción con fármacos y medicamentos que esté usando. Además, pueden presentarse otros efectos secundarios graves desconocidos, incluso la muerte.

Todas estas ocurrencias se registrarán, y los investigadores y enfermeros le explicarán determinadas medidas para limitarlas. Durante el desarrollo del estudio, un equipo de investigadores y enfermeros capacitados supervisará su salud y su seguridad.

Si experimenta alguno de los efectos secundarios mencionados más arriba u otros síntomas, debe comunicárselo al médico o al personal del estudio de inmediato. Si no le proporciona al médico o al personal del estudio esta información relacionada con cualquier efecto secundario, al participar en este estudio podría ocasionarse involuntariamente un daño.

Si tiene preguntas sobre los signos o síntomas de los efectos secundarios que leyó en este formulario de consentimiento, hágaselas al médico del estudio.

Para reducir la posibilidad de lesiones, siempre use el dispositivo de acuerdo con las instrucciones del fabricante. Las advertencias y las instrucciones de seguridad incluidas en el Manual del usuario no cubren todos los posibles problemas médicos y las situaciones que podrían ocurrir. Consulte el Manual del usuario para obtener más información.

RIESGOS DE LOS PROCEDIMIENTOS DEL ESTUDIO

Durante la obtención de las muestras de sangre, es posible que experimente dolor y/o la formación de moretones en el sitio en que se inserta la aguja/el catéter o el lugar donde se coloca el brazalete para medir la presión arterial. Aunque es raro, puede haber

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formación localizada de coágulos, daños en los nervios e infecciones. También puede experimentar sensación de desvanecimiento y/o desmayos durante la extracción de sangre o poco después.

Los electrodos del ECG pueden causar una reacción en la piel, como enrojecimiento o picazón. Usted también puede presentar molestias en la piel y/o pérdida de vello localizadas asociadas con la colocación de los electrodos del ECG.

Radiografías: si es necesario realizar una radiografía del pecho durante el proceso de selección para este estudio, la exposición a la radiación de una radiografía equivale a aproximadamente 3 días de exposición a la radiación ambiental natural.

Espirometría: para este procedimiento se usará un broncodilatador de acción rápida (medicamento para abrir los bronquios). Es posible que haya un riesgo pequeño de una reacción adversa a este medicamento (como la sensación de que el corazón late más rápido [palpitaciones] o temblores/sacudidas leves). Debe comunicarle al médico del estudio de inmediato cualquier síntoma que pueda experimentar mientras usa este medicamento. Los procedimientos se llevarán a cabo según las normas internacional y científicamente aceptadas.

RIESGOS DESCONOCIDOS/IMPREVISIBLES

Además de los riesgos mencionados anteriormente, pueden existir algunos riesgos desconocidos, poco frecuentes e imprevisibles asociados al uso de estos productos, que incluyen reacciones alérgicas graves o que ponen en riesgo la vida, o interacciones inesperadas con otro medicamento. Se le comunicará oportunamente, tanto en forma oral como escrita, toda nueva información, hallazgo o cambio en la forma en que se llevará a cabo la investigación que pudiera influir sobre su deseo de seguir participando en este estudio.

Si sufre una lesión, un efecto malo o cualquier otra experiencia de salud inusual durante este estudio, debe comunicarse con el médico o el personal del estudio de inmediato.

RIESGOS PARA UN BEBÉ EN GESTACIÓN

Riesgos en el embarazo/para el feto: se sabe que los efectos de fumar para un niño en gestación son dañinos. No debe estar embarazada para participar en este estudio. Es importante que use los siguientes métodos anticonceptivos adecuados durante todo el estudio y hasta la finalización del período de seguimiento de seguridad, y que las mujeres no queden embarazadas ni amamenten a un bebé.

- Dispositivo o sistema intrauterino (DIU).
- Uso establecido de métodos hormonales orales/inyectables/implantables/transdérmicos.
- Métodos anticonceptivos de barrera.
 - Preservativos o capuchones oclusivos (diafragma) con espuma/gel/película/supositorio espermicida.

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- Pareja(s) que se haya(n) realizado una vasectomía.
- Abstinencia verdadera (la abstinencia periódica y el coito interrumpido no son métodos eficaces).

No es necesario usar anticonceptivos, si se ha practicado histerectomía, ligadura de trompas, ovariectomía bilateral o si es posmenopáusica. El estado posmenopáusico se define como mujeres que no han tenido ciclos menstruales durante más de 12 meses. Se debe realizar una prueba de la hormona foliculoestimulante, cuyo resultado debe estar dentro de los límites aceptables.

Si cree que ha quedado embarazada durante el estudio, es importante que se lo comunique al médico del estudio de inmediato. Si queda embarazada o cree que puede estar embarazada, será retirada del estudio y el médico del estudio la derivará para que reciba atención obstétrica. El costo de esa atención será responsabilidad suya. Es posible que el médico del estudio le pida hacer un seguimiento de su embarazo, y le informará al patrocinador y al Comité de Revisión Independiente (*Independent Review Board*, IRB) sobre el embarazo y su desenlace.

BENEFICIOS

La participación en este estudio tiene fines exclusivamente de investigación y no mejorará su salud ni tratará cualquier problema médico que pueda tener. Puede beneficiarse por la realización de las exploraciones físicas. Los resultados de los análisis de laboratorio realizados durante la visita de selección se pondrán a su disposición si lo solicita. Sin embargo, si usted no reúne los requisitos para participar en el estudio según otros procedimientos de selección, es posible que no se realicen algunos análisis de laboratorio.

Este estudio se realiza únicamente con fines de investigación. No hay ningún beneficio directo para usted por participar en el estudio, excepto que recibirá un examen de la salud y asesoramiento para dejar de fumar. Los resultados del estudio ayudarán al patrocinador a comprender mejor la seguridad del producto THS 2.2 Menthol y qué tan bien el cuerpo absorbe la nicotina que contiene el producto. Esta información puede ayudar a otras personas en el futuro.

ALTERNATIVAS AL TRATAMIENTO

En este estudio, no se administra ningún medicamento en estudio. Por lo tanto, no hay ningún tratamiento alternativo que corresponda como parte de este estudio. Sin embargo, si decide que desea dejar de fumar, el personal del estudio le proporcionará información sobre cómo buscar ayuda para hacerlo.

COSTO

Participar en este estudio de investigación no implica ningún costo. El producto THS 2.2 Menthol, los procedimientos relacionados con el estudio y las visitas del estudio se proporcionarán sin cargo para usted ni para su compañía de seguros.

COMPENSACIÓN POR PARTICIPAR EN ESTE ESTUDIO

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Será compensado por participar en este estudio de investigación según lo detallado a continuación. Esta compensación es por su tiempo y los inconvenientes causados. Recibirá una compensación según el siguiente programa.

Programa de compensación

Visita de selección	-0-
Visita de selección para realizar una radiografía del pecho	\$50.00
Noches de internamiento en el centro de investigación (11 noches x \$250.00)	\$2750.00
Visita extendida como paciente ambulatorio (3 visitas x \$200)	\$600.00
Diarios (por semana), 14 semanas x \$100	\$1400.00
Finalización del estudio	\$720.00
TOTAL	\$5520.00

La compensación total del estudio completo será de \$5520. Si elige retirarse del estudio de investigación, recibirá una compensación solamente por la parte del estudio que haya completado según lo detallado más arriba. Si Covance debe comprarle cigarrillos mentolados convencionales porque se le acabaron durante el período de confinamiento, la cantidad que se haya gastado se deducirá del total de su compensación.

Si se retira del estudio de forma anticipada debido a un evento médico importante o si el patrocinador cancela el estudio, recibirá una compensación de un importe correspondiente a la parte de la compensación del estudio completo en función de la cantidad de visitas que haya realizado.

Si es seleccionado como un suplente y no es seleccionado para participar en el estudio, recibirá una compensación de \$250.00 para cada noche. Si como suplente obtiene un resultado positivo en las pruebas de detección de cualquier droga no autorizada o de alcohol, no recibirá ninguna compensación.

Todos los participantes de la investigación recibirán su compensación dentro de los 21 días posteriores a la finalización de su participación en el estudio.

Si participa en este estudio, acepta que no será considerado un empleado de Covance o de Philip Morris Products S.A.

No se deducen impuestos de su cheque. Usted es responsable del pago de cualquier impuesto estatal, federal o de seguro social. Deberá proporcionarle a Covance su número de seguro social o número de identificación fiscal, si lo tiene. Si recibe de Covance más de \$600 en un año calendario, se le entregará el formulario de impuestos 1099 en el siguiente mes de enero. Covance comunica el dinero que usted recibe al

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Servicio de Impuestos Internos (*Internal Revenue Service*, IRS).

Si no tiene un número de seguro social o un número de identificación fiscal, el Servicio de Impuestos Internos (IRS) le exige a Covance deducir el 30% de su compensación. Deberá seguir la normativa del IRS para determinar si es elegible para recibir un reembolso, o bien, comunicarse con un contador especializado en impuestos para que le ayude.

DERECHO A RETIRARSE O SER RETIRADO DEL ESTUDIO

Su participación en este estudio es voluntaria. Usted es libre de retirarse de este estudio en cualquier momento; sin embargo, debe comunicarle inmediatamente al médico del estudio si tiene previsto retirarse. Su decisión de participar en este estudio o de retirarse de él no influirá sobre la disponibilidad de su atención médica futura y no implicará sanciones ni pérdida de los beneficios a los que tenga derecho. Puede retirarse de este estudio en cualquier momento. Puede retirar su consentimiento para usar y divulgar su información en cualquier momento. Si usted retira su consentimiento, no podrá seguir participando en este estudio. Si por cualquier motivo se retira o abandona el estudio de forma anticipada, se le pedirá que complete los procedimientos del alta del día 6.

El patrocinador del estudio o el médico a cargo del estudio pueden retirarlo de este estudio sin su consentimiento por cualquier motivo, entre otros:

- El patrocinador o el médico del estudio consideran que un problema médico o una circunstancia puede poner en peligro su bienestar o la integridad del estudio.
- Si usted no sigue las instrucciones del equipo del estudio.
- Si el patrocinador y/o los médicos que participan en el estudio detienen el estudio antes de su finalización o el patrocinador pide que se lo retire del estudio.

CONFIDENCIALIDAD

Si acepta participar en el estudio de investigación, el personal del estudio reunirá, registrará y almacenará información sobre su identidad, salud y participación.

El patrocinador y sus representantes, la Administración de Alimentos y Medicamentos (FDA) de los Estados Unidos, otras autoridades de salud y el Comité de Revisión Independiente MidLands pueden inspeccionar sus registros médicos en papel o en forma electrónica que posiblemente incluyan su nombre, dirección y otra información personal que permita identificarlo. Si fuera necesario, se pueden copiar todos sus registros médicos o parte de ellos durante estas inspecciones.

Los resultados de este estudio de investigación pueden presentarse en conferencias o pueden incluirse en publicaciones. Sin embargo, usted no será identificado

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personalmente en ninguna presentación o publicación.

Debido a la necesidad de usar información según lo observado más arriba, no se puede garantizar la confidencialidad absoluta.

Habrà una descripción de este ensayo clínico disponible en www.ClinicalTrials.gov, según lo exigen las leyes de los Estados Unidos. Este sitio web no incluirà información que pueda identificarlo. A lo sumo, incluirà un resumen de los resultados. Puede consultar este sitio web en cualquier momento.

CONFIDENCIALIDAD COMERCIAL

La información y todo material o artículo que se le entregue relacionado con el estudio o durante el estudio, como información que permite identificar la unidad de investigación, el patrocinador, cualquier producto del estudio y/o el tipo de estudio que se está realizando, se deberá considerar información comercial confidencial de Covance y el patrocinador del estudio. Por supuesto que usted es libre de analizar esta información confidencial con otras personas, como su médico o sus amigos y familiares, para considerar la posibilidad de participar o no en este estudio o en cualquier momento en que analice su atención médica presente o futura, o sus derechos. Sin embargo, se prohíbe la distribución de información comercial confidencial según lo descrito más arriba en cualquier medio de comunicación o su publicación en Internet.

¿QUIÉN ORGANIZA ESTA INVESTIGACIÓN?

La empresa que patrocina este estudio es Philip Morris Products S.A., Suiza (incluidos los agentes, contratistas o consultores).

¿QUIÉN HA REVISADO EL ESTUDIO?

El Comité de Revisión Independiente MidLands (MLIRB) ha revisado los objetivos y la realización propuesta del estudio principal.

EN CASO DE LESIONES

Su seguridad es la principal preocupación de cada miembro del personal. Comuníquese con el personal del estudio lo antes posible si tiene efectos secundarios o lesiones. El número de teléfono de Covance Dallas Clinical Research Unit es 214-920-9053.

Covance le proporcionará tratamiento médico inmediato, sin costo para usted, por los efectos secundarios o las lesiones que hayan sido causadas por participar en este estudio. Los gastos médicos en los que incurra por cualquier lesión relacionada con la investigación, diferentes de los costos del tratamiento médico inmediato, serán responsabilidad suya o de un tercero pagador. No se le impide que busque obtener compensación por una lesión relacionada con negligencia, fallas, o culpa de las personas involucradas en la investigación.

Al firmar este formulario de consentimiento, usted **NO RENUNCIA** a ninguno de sus

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derechos legales.

CONTACTO DE EMERGENCIA

Si durante el estudio experimenta cualquier problema médico o sufre una lesión relacionada con la investigación, comuníquese con el médico del estudio llamando al número de teléfono que figura en la página uno de este documento de consentimiento. Si busca atención de emergencia o requiere internamiento, comuníquelo al médico que lo trate que usted está participando en un estudio de investigación dirigido por el médico del estudio que se menciona en la página uno de este documento.

PERSONAS QUE DEBEN CONTACTARSE PARA PREGUNTAS, PREOCUPACIONES O QUEJAS

Si tiene alguna pregunta o algún problema, si cree que puede haber sufrido una lesión relacionada con la investigación, o si tiene preguntas sobre la disponibilidad de atención médica, debe comunicarse con el Dr. William Lewis llamando al 214-920-9053.

Si tiene preguntas sobre sus derechos, preguntas generales, quejas o preocupaciones sobre esta investigación, o preguntas sobre sus derechos como una persona que participa en este estudio, llame al Comité de Revisión Independiente MidLands (MLIRB) al (913) 385-1414 o al (800) 636-4445. Si en cualquier momento durante o después de su participación en esta investigación, le gustaría recibir información u ofrecer datos sobre su experiencia en la investigación, puede llamar al IRB MidLands al número que figura más arriba o puede visitar el sitio web del IRB MidLands en www.mlirb.com y enviarnos sus comentarios. En cualquier caso, no tiene que darnos su nombre, si no lo desea.

Usted tiene derecho a hacer cualquier pregunta sobre los peligros potenciales y/o conocidos de este estudio en cualquier momento. Si tiene cualquier pregunta sobre su participación en este estudio, o si en cualquier momento cree haber experimentado una lesión relacionada con la investigación o una reacción al medicamento del estudio, comuníquese con el Dr. William Lewis llamando al 214-920-9053.

DERECHOS LEGALES

Al firmar este formulario de consentimiento, usted no perderá ninguno de sus derechos legales a los que tenga derecho de otro modo.

DECLARACIÓN DE CIERRE

Usted ha leído cuidadosamente la información anterior. Además, ha recibido respuestas satisfactorias a todas las preguntas que ha hecho y firma voluntariamente este formulario de consentimiento. Recibirá una copia del documento de consentimiento informado firmado. Por la presente, acepta voluntariamente participar en este estudio.

Puede retirar este consentimiento en cualquier momento.

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**NOTIFICACIÓN AL MÉDICO DE CABECERA**

Después de que se hayan realizado todas las pruebas de elegibilidad y se haya determinado que usted es apto para ingresar en el estudio, si lo desea, le comunicaremos a su médico particular que está participando en este estudio de investigación. Marque su preferencia a continuación.

- ☐ Sí, quiero que el médico del estudio le informe a mi médico particular acerca de mi participación en este estudio.

Nombre, dirección y número de teléfono del médico particular

- ☐ No, no quiero que el médico del estudio le informe a mi médico particular acerca de mi participación en este estudio.
- ☐ No tengo un médico particular.

**FIRMAS****Lea el párrafo siguiente en voz alta a la persona que obtiene el consentimiento.**

- He leído la información anterior en un idioma que comprendo bien.
- Me han explicado el contenido y el significado de esta información.
- He tenido la oportunidad de hacer mis preguntas en privado así como reunirme con un médico del estudio para analizar este estudio.
- He hecho al personal las preguntas que pueda haber tenido y he tenido tiempo suficiente para decidir si quiero participar en este estudio.
- Por medio del presente, acepto y me ofrezco voluntariamente a participar en este estudio, y autorizo el uso y la divulgación de información médica sobre mi persona.
- También acepto que se realicen las pruebas de VIH descritas en este documento.
- Dono voluntaria y libremente todas las muestras de sangre y orina para la investigación descrita más arriba, y por el presente, renuncio a todos los derechos de propiedad, título e interés que pueda tener sobre esas muestras.
- Acepto mantener la confidencialidad de toda la información relacionada con el producto del estudio (THS 2.2 Menthol), que incluye el diseño del producto, las especificaciones y el método de funcionamiento.

Nombre del participante en letra de imprenta

Firma del participante

Fecha

Hora

Nombre en letra de imprenta de la
persona que realiza el análisis del
consentimiento informado
y la verificación del alfabetismoFirma de la persona que
realiza el análisis del
consentimiento informado
y la verificación del alfabetismo

Fecha

Hora

He recibido una copia firmada y fechada del formulario de consentimiento de este estudio para que la guarde.**Su firma****Fecha**

Para completar únicamente por el personal de Covance:

QC'd by _____

Date

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**AUTORIZACIÓN Y CONSENTIMIENTO PARA USAR Y DIVULGAR
INFORMACIÓN DE SALUD PROTEGIDA PARA INVESTIGACIÓN**

Durante su participación en este estudio de investigación, el médico y el personal del estudio obtendrán o generarán información médica personal sobre usted (por ejemplo, registros médicos y resultados de todas las pruebas, los exámenes o los procedimientos que se realicen mientras participa en el estudio) y la registrarán en documentos del estudio. El médico del estudio conservará esta información médica de salud personal en sus registros relacionados con el estudio (a los que haremos referencia como "sus registros del estudio"). Además, el médico del estudio puede obtener, e incluir en sus registros, información sobre su salud y/o sus problemas físicos o mentales pasados, presentes y/o futuros. Es posible que el médico del estudio le pida que firme otra autorización para obtener parte o todos sus registros médicos de su médico. Sus registros del estudio pueden incluir otra información personal (como el número de seguro social, números de registros médicos, fecha de nacimiento, etc.), que podrían usarse para identificarlo. La información de la salud que podría identificarlo se llama "información de salud protegida" (*protected health information*, PHI).

Cuando corresponda de acuerdo con las leyes federales (la "Norma de privacidad") u otras leyes vigentes, su PHI creada u obtenida durante este estudio de investigación no podrá "usarse" para realizar la investigación ni "divulgarse" (entregarse a ninguna persona o entidad) con fines de investigación sin su permiso o consentimiento. Este permiso y consentimiento se llama "autorización". Por lo tanto, usted no puede participar en este estudio a menos que dé su permiso para usar y divulgar su PHI firmando esta autorización. Al firmar, está aceptando permitir al médico y al personal del estudio el uso de su PHI para llevar a cabo este estudio.

Al firmar esta autorización, usted también está aceptando permitir al médico y al personal del estudio que divulguen su PHI a las personas y los grupos que se describen a continuación:

- El patrocinador de este estudio (PATROCINADOR) y cualquier persona que trabaje en representación del patrocinador para llevar a cabo este estudio (a quienes se hace referencia como "el patrocinador"). El patrocinador analizará y evaluará la PHI, y puede usarla para desarrollar nuevas pruebas, procedimientos y productos comerciales. El personal del estudio le asignará un código numérico y/o letras a sus registros, lo que significa que usted no será habitualmente identificado en los registros que se envíen al patrocinador. Sin embargo, el patrocinador podrá ver sus registros completos del estudio o recibir información relacionada con las muestras que lo identifican. Además, el patrocinador puede visitar el centro del estudio para supervisar la forma en que se está efectuando el estudio, y puede revisar su PHI durante estas visitas, para asegurarse de que la información sea correcta.
- El Comité de Revisión Independiente ("IRB") puede tener acceso a su PHI en relación con sus responsabilidades como Comité de Revisión Institucional.

El médico o el patrocinador del estudio pueden divulgar su PHI a la Administración de

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Alimentos y Medicamentos ("FDA") de los Estados Unidos u organismos reguladores similares en Estados Unidos y/o países extranjeros.

Estas divulgaciones también ayudan a asegurar que la información relacionada con la investigación esté disponible para todas las partes que puedan necesitarla con fines de investigación.

Excepto las divulgaciones descritas anteriormente, su PHI no se compartirá con otras personas o entidades a menos que lo requiera la ley. Si su PHI se entrega a las partes mencionadas anteriormente y/o a otras personas o entidades que no están obligadas a cumplir las leyes vigentes, es posible que su PHI ya no esté protegida por estas leyes y posiblemente se use o divulgue de maneras diferentes a las descritas aquí.

Tiene derecho a ver y a hacer copias de su PHI. Sin embargo, al firmar este documento, usted acepta que no podrá ver ni copiar su PHI, ya sea total o parcialmente, hasta que el patrocinador haya completado todo el trabajo relacionado con este estudio. En ese momento, podrá pedir ver sus registros.

Esta autorización no tiene fecha de vencimiento a partir de la fecha en que la firme, a menos que la revoque (cancele o retire) antes.

Tiene derecho a revocar su autorización en cualquier momento. Si la revoca, su PHI dejará de usarse para este estudio, excepto en la medida en que las partes vinculadas con la investigación ya hubieran actuado teniendo en cuenta su autorización o necesiten la información para completar análisis e informes de esta investigación. Para revocar su autorización, debe escribir al médico del estudio a la dirección que figura en la primera página de este formulario, manifestando que revoca su autorización para el uso y la divulgación de la información de salud protegida. Si revoca esta autorización, no podrá continuar participando en este estudio.

Recibirá una copia de esta autorización fechada y firmada después de que la haya firmado.

Firma del sujeto

Fecha

Nombre del sujeto en letra de imprenta

Firma de la persona que obtiene la autorización

Fecha

APPROVED BY

APR 28 2014

MLIRB
Midlands Independent Review Board

Nombre en letra de imprenta de la persona que obtiene la autorización

Para completar únicamente por el personal de Covance:

QC'd by _____

Date _____

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16.1.3.19.2 INFORMED CONSENT DOCUMENT FOR GENETIC AND
PHARMACOGENOMIC ANALYSIS

**DOCUMENTO DE CONSENTIMIENTO INFORMADO PARA ANÁLISIS GENÉTICO Y FARMACOGENÓMICO**

Título del estudio. Estudio aleatorizado, controlado, abierto, multicéntrico, de 3 grupos paralelos, para demostrar las reducciones en la exposición a constituyentes del humo seleccionados en fumadores aparentemente sanos que cambian al sistema de calentamiento de tabaco mentolado 2.2 (THS 2.2 Menthol) o dejan de fumar, en comparación con continuar usando cigarrillos mentolados convencionales, durante 5 días en internamiento y 86 días más en un contexto ambulatorio.

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Número de selección del sujeto:	<input type="text"/>
Investigador principal: (Médico del estudio)	Covance Dallas Site Dr. William Lewis
Dirección del centro de investigación:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Número de teléfono:	Covance Dallas Site Tel.: 214-920-9053
Número de teléfono las 24 horas:	Covance Dallas Site Tel.: 972-955-5373
Patrocinador:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Suiza

INTRODUCCIÓN

Usted ya ha aceptado participar en el "Estudio de exposición reducida usando THS 2.2" (el estudio principal), relacionado con el nuevo sistema de calentamiento de tabaco 2.2 (THS 2.2) para la evaluación de los efectos de THS 2.2, un nuevo producto de tabaco de riesgo modificado, sobre los marcadores biológicos (biomarcadores) de exposición seleccionados en comparación con los cigarrillos normales (convencionales).

Este formulario de consentimiento del estudio secundario le informa sobre evaluaciones opcionales que se llevarán a cabo en sujetos que aceptaron participar en el estudio principal. Este formulario de consentimiento informado e información para el sujeto es una adición al

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formulario de consentimiento del estudio principal que ya ha firmado. La intención de este documento es ofrecerle información, de forma que pueda decidir si quiere participar en este estudio secundario opcional.

Se le pide que permita la recogida de una muestra de su sangre así como muestras nasales y bucales (de la boca). Se realizarán análisis genéticos con estas muestras. Permitir que se extraigan estas muestras para realizar esta investigación genética es totalmente voluntario. No tiene que aceptar participar en el estudio de investigación genética para participar en el estudio principal.

El médico o el personal del estudio le explicarán todos los procedimientos y responderán cualquier pregunta que pueda tener respecto a este estudio secundario de investigación. Si acepta participar como voluntario, se le pedirá que firme y feche este formulario de consentimiento y se le entregará una copia para que la conserve. Si no acepta participar en el estudio de investigación genética, puede seguir participando en el estudio principal.

Debe haber revisado y firmado el consentimiento informado del estudio principal antes de revisar este formulario de consentimiento.

Este formulario no está pensado para reemplazar al del estudio principal, y el contenido del formulario de consentimiento informado del estudio principal explica el objetivo general de esta investigación y las condiciones de su participación en el estudio principal.

Al firmar este formulario de consentimiento, usted acepta la recogida y el almacenamiento de muestras de sangre, nasales y bucales para realizar análisis farmacogenómicos. La farmacogenómica evalúa el modo en que su estructura genética específica maneja un medicamento.

Este formulario puede contener palabras que usted no comprenda. Pida al médico o al personal del estudio que le expliquen todas las palabras o la información que no entienda con claridad antes de aceptar participar como voluntario en este estudio secundario. Antes de que decida participar, debe entender el objetivo de este estudio secundario opcional, cualquier posible riesgo para usted y lo que se espera de usted durante este estudio secundario. Incluso si acepta participar en este estudio secundario opcional puede cambiar de idea y dejarlo en cualquier momento sin sufrir ninguna penalización ni pérdida de beneficios.

¿QUIÉN ORGANIZA LA INVESTIGACIÓN?

La empresa que patrocina este estudio secundario opcional es Philip Morris Products S.A., Suiza (incluidos agentes, contratistas o consultores). Philip Morris Products S.A. es un fabricante de productos de tabaco. Como se explica en el consentimiento informado del estudio principal, el patrocinador está desarrollando un método alternativo a los cigarrillos convencionales (normales), al desarrollar un producto que puede tener el potencial de reducir algunos de los riesgos de las enfermedades relacionadas con el tabaco.

**CONFIDENCIALIDAD EMPRESARIAL**

La información y cualquier material o artículo que se le entregue sobre o durante el estudio, como información de identificación de la unidad de investigación, el patrocinador y los productos de estudio, y el tipo de estudio que se está realizando, debe considerarse información empresarial confidencial de Covance y el patrocinador del estudio. Por supuesto, tiene la libertad de comentar dicha información de forma confidencial con otros, como su médico o amigos o familiares, con el objetivo de considerar si participar en este estudio o, en cualquier momento, al comentar sus derechos o su atención médica presente o futura. Sin embargo, está prohibida la distribución de información empresarial confidencial, tal como se describe anteriormente, a los medios de comunicación, al igual que su publicación en Internet.

NATURALEZA Y OBJETIVO

Cuando las personas se exponen a sustancias o una mezcla de sustancias (p. ej., alimentos, humo, medicamentos) pueden desencadenarse reacciones en el cuerpo. Estas reacciones o respuestas variarán de una persona a otra, dado que cada persona tiene un material genético (genes) diferente.

Una vez que el organismo absorbe la sustancia, podría afectar al nivel de expresión de estos genes. Estos genes podrían entonces influir en el tiempo que algunas de las sustancias pueden permanecer en el organismo, cómo se descomponen o por qué algunas personas podrían reaccionar de forma diferente a ellas.

Las células son los componentes con los que se construye el cuerpo humano y cada tipo de célula está especialmente adaptada a su función específica en el cuerpo. Todas las células contienen proteínas que se producen a partir de una sustancia llamada ácido ribonucleico mensajero (ARNm) y que permite que las células funcionen.

El objetivo de este estudio secundario es obtener muestras de sangre, nasales y bucales para análisis e investigaciones sobre cómo responderán los fumadores al aerosol (humo) generado por el producto THS 2.2., en comparación con los sujetos expuestos al humo de cigarrillos convencionales, o en comparación con un grupo de sujetos que han dejado de fumar.

La evaluación de estas diferencias puede brindar información sobre los procesos biológicos que se producen al usar el producto del estudio en comparación con el consumo de cigarrillos convencionales o dejar de fumar. También nos permitirá comparar si hay diferencias en el nivel de expresión de estos genes en un fumador entre la boca y la nariz.

Las muestras también se recopilarán para determinar la cantidad y la calidad del ARN (farmacogenómica) en muestras de sangre para comprender si el efecto nocivo de fumar cigarrillos convencionales sobre la función celular podría reducirse al cambiar al producto de prueba o al dejar de fumar.

PROCEDIMIENTOS DEL ESTUDIO

Si acepta participar en este estudio secundario, se le realizarán los tres siguientes procedimientos de recogida de muestras adicionales:

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Procedimiento de recogida de muestra epitelial nasal ("recogida de células de la nariz") (Días 0, 6 y 90)

Se le pedirá que se suene la nariz. Este procedimiento se realizará solo en el orificio nasal izquierdo. Si desea que le adormezcan el orificio nasal para el procedimiento, se utilizará un spray anestésico con lidocaína al 1 %. Se introducirá un espéculo nasal (dispositivo parecido a unas pinzas) para ampliar el orificio nasal izquierdo y luego se introducirá un cepillo suave en el orificio nasal y se presionará y girará contra la parte exterior del orificio nasal durante unos 3 segundos, antes de retirarlo. Se introducirá un segundo cepillo suave en el mismo orificio nasal y se presionará y girará contra la parte exterior del orificio nasal durante unos 3 segundos, antes de retirarlo.

Procedimiento de recogida de muestra bucal ("recogida de células de la boca") (Días 0, 6 y 90)

Se le pedirá que se enjuague la boca con agua (unas 4 cucharaditas, 20 ml) que le proporcionaremos. Se introducirá un cepillo estéril en su boca y se presionará ligeramente contra el lateral de su boca (cara interna de la mejilla) hasta que se doble el eje. El cepillo se girará entonces durante unos 10 segundos y se repetirá el procedimiento en la otra mejilla.

Recogida de sangre para transcriptómica (Días 0 y 90)

Se extraerán tres muestras de sangre adicionales para este tipo de análisis (unas 3 cucharaditas, 15 ml en total). Específicamente, se requerirá una muestra de sangre al inicio del estudio en el Día 0, una segunda muestra de sangre en el Día 6 y una tercera muestra al final del estudio en el Día 91.

RIESGOS DE LOS PROCEDIMIENTOS DEL ESTUDIO

Durante la recogida de muestras nasales y bucales, los efectos secundarios que pueden producirse incluyen ardor, dolor, picazón e irritación nasal. En raras ocasiones, puede producirse sangrado de la nariz. Si decide que quiere que le adormezcan los orificios nasales, el spray de lidocaína puede provocar algunas reacciones alérgicas y adormecimiento. Si se utiliza indebidamente, la lidocaína puede provocar efectos secundarios graves como dificultad para respirar, inflamación de la boca o la cara y dolor de pecho.

Durante la recogida de las muestras de sangre, es posible que experimente dolor y/o la formación de moretones en el sitio en que se inserta la aguja/el catéter o en la ubicación del manguito para medir la presión arterial. Aunque es raro, se pueden formar coágulos localizados, producirse daños en los nervios e infecciones. También puede experimentar sensación de desvanecimiento o mareo y/o un desmayo durante la extracción de sangre o poco después.

Los posibles riesgos de la participación en el estudio principal se describen en el documento de consentimiento informado del estudio.

OTROS POSIBLES RIESGOS

Existen posibles riesgos no físicos asociados con esta investigación genética, como los riesgos asociados con una violación de la privacidad o la confidencialidad. La violación de la confidencialidad, puede generar discriminación en las áreas de empleo y seguros, estigmatización social o estrés psicológico provocado por la divulgación de información adversa para usted o su familia. Aunque se supone que estas pruebas son privadas, esto no



se puede garantizar. Por ejemplo, es posible que un tribunal obtenga registros médico o del estudio sin su permiso.

CONFIDENCIALIDAD

Todas sus muestras llevarán un código. Este código contendrá su edad, sexo, raza y otra información. No contendrá su nombre ni sus iniciales. Mientras las muestras se conserven en el centro del estudio principal podrán asociarse con usted. Antes de enviar las muestras fuera del centro del estudio principal a un laboratorio externo para que realice análisis, se anonimizarán. Esto significa que se eliminará la vinculación entre usted y el código de la muestra y no será posible asociar las muestras con usted. La anonimización está prevista para evitar su reidentificación.

Las muestras se enviarán al laboratorio externo para que su análisis después de que se hayan introducido todos los demás datos recopilados durante el estudio principal (aproximadamente 3-4 meses después de que el último voluntario complete el estudio). Como no se pueden vincular con usted las muestras anonimizadas y los datos asociados, no es posible tomar medidas como retirar una muestra, o devolver resultados individuales, aunque nos lo solicite, si la solicitud se hace después de que las muestras se envíen para análisis desde el centro del estudio.

RETIRADA DE LAS MUESTRAS

Como se explicó anteriormente, usted decide libremente si quiere participar en este estudio secundario. Puede dejar de entregar muestras biológicas en cualquier momento. Su decisión de interrumpir su participación en este estudio secundario no afecta a su participación en el estudio principal.

Su médico del estudio principal conservará registros que asocien su información personal con sus muestras codificadas hasta el envío de las muestras a un laboratorio externo para su análisis. Antes de que las muestras abandonen el centro del estudio, se eliminará el vínculo que las asocia con usted. Si retira su consentimiento para el estudio secundario antes de la eliminación de este vínculo, puede solicitar que los investigadores destruyan las muestras y dejen de utilizarse en la investigación. Si retira su consentimiento después de que las muestras abandonen el centro del estudio, no habrá posibilidad de asociarlas con usted y, por tanto, no será posible destruirlas ni excluir esas muestras de análisis futuros.

El patrocinador y los investigadores que trabajan en su nombre tienen derecho a conservar y usar cualquier resultado de investigación que obtengan de las muestras que se recopilaron antes de su retirada del consentimiento.

BENEFICIOS

Puede que no haya un beneficio directo para usted por su participación en este estudio. Sin embargo, su participación puede ayudar a mejorar el conocimiento y la comprensión de enfermedades médicas y el modo en que la gente responde a los productos del estudio.

Los investigadores no se comunicarán con usted ni con el médico del estudio en relación con la investigación ni con ninguna información sobre los resultados de las pruebas realizadas en las muestras de este estudio secundario.

ALTERNATIVA

Usted tiene la opción de no participar en este estudio secundario opcional.

N.º de versión: 2

Aprobado por MLIRB el 04/22/14

N.º de protocolo: ZRHM-REXA-08-US

ZRHM-REXA-08-US Spanish CONSENT_PHARMACOGENOMIC for US version 1.0 dated 21-Apr-2014

**COMPENSACIÓN POR PARTICIPAR EN ESTE ESTUDIO**

La compensación total por este estudio secundario opcional será de \$150.

DESARROLLO DE GANANCIA COMERCIAL

Aunque la investigación futura que use sus muestras puede llevar al desarrollo de nuevos productos, usted no recibirá ninguna compensación por estos nuevos productos. Al aceptar esta investigación, usted renuncia a reclamar cualquier dinero obtenido por los investigadores como consecuencia del uso comercial o de otro tipo de estas muestras.

¿QUIÉN HA REVISADO EL ESTUDIO?

El Comité de Revisión Independiente MLIRB ha revisado los objetivos y la realización prevista del estudio principal.

EN CASO DE LESIONES

Su seguridad es la principal preocupación de todos los miembros del personal del estudio. Comuníquese con el personal del estudio lo antes posible si tiene algún efecto secundario o lesión. Su número de teléfono es 214-920-9053.

El personal del estudio brindará tratamiento médico inmediato, sin costo para usted, para efectos secundarios o lesiones provocados por participar en este estudio. Al margen de los costos del tratamiento médico inmediato, los gastos médicos de cualquier lesión relacionada con la investigación serán responsabilidad de usted o de su tercero pagador, aunque esto no le impide buscar una compensación por una lesión relacionada con una negligencia, falla o culpa por parte de las personas implicadas en la investigación.

PERSONAS QUE DEBEN CONTACTARSE PARA PREGUNTAS, PREOCUPACIONES O QUEJAS

Si tiene alguna pregunta o algún problema, si cree que puede haber sufrido una lesión relacionada con la investigación, o si tiene preguntas sobre la disponibilidad de atención médica, debe comunicarse con el Dr. William Lewis llamando al 214-920-9053.

Si tiene preguntas sobre sus derechos, preguntas generales, quejas o preocupaciones sobre esta investigación, o preguntas sobre sus derechos como una persona que participa en este estudio, llame al Comité de Revisión Independiente MidLands (MLIRB) al (913) 385-1414 o al (800) 636-4445. Si, en cualquier momento durante o después de su participación en esta investigación, desea información u ofrece comentarios sobre su experiencia con la investigación, puede llamar al IRB MidLands al número de teléfono anterior o puede entrar en el sitio web del IRB MidLands en www.mlirb.com y dejarnos sus comentarios. En cualquier caso, no tiene que darnos su nombre si no desea hacerlo.

Tiene derecho a realizar preguntas en cualquier momento sobre los posibles riesgos o riesgos conocidos de este estudio. Si tiene alguna pregunta relativa a su participación en este estudio, o si en cualquier momento siente que ha experimentado una lesión relacionada con la investigación o una reacción al medicamento del estudio, comuníquese con el Dr. William Lewis llamando al 214-920-9053.

**DERECHOS LEGALES**

Al firmar este formulario de consentimiento, usted no perderá ninguno de los derechos legales a los que de otro modo tiene derecho.

CONSENTIMIENTO Y FIRMAS**Lea el siguiente párrafo en alto a la persona que obtiene el consentimiento.**

He leído la información anterior en un idioma que entiendo bien. Se me ha explicado el contenido y el significado de esta información.

Se me ha ofrecido la oportunidad de realizar preguntas en privado, así como de reunirme con el médico del estudio para comentar este estudio.

He realizado al personal todas las preguntas que tenía y he tenido suficiente tiempo para decidir si deseo participar en este estudio secundario.

Por el presente, acepto voluntariamente y me ofrezco a participar en este estudio y autorizo el uso y la divulgación de mi información médica.

Dono libre y voluntariamente todas y cada una de las muestras biológicas para la investigación que se describen anteriormente y, por el presente, renuncio a todo derecho de propiedad, título e interés que pueda tener sobre esas muestras.

Nombre del participante en letra
de imprenta

Firma del participante

Fecha

Hora

Nombre de la persona que obtiene
el consentimiento informado y la
verificación de que el sujeto sabe leer
en letra de imprenta

Firma de la persona que obtiene el
el consentimiento informado y la
verificación de que el sujeto sabe leer

Fecha

Hora

Recibiré una copia de este formulario de consentimiento del estudio firmado y fechado para conservarla.

Su firma

Fecha

A completar solo por el personal de Covance:

Control de calidad realizado por _____

Fecha _____

N.º de versión: 2

Aprobado por MLIRB el 04/22/14

N.º de protocolo: ZRHM-REXA-08-US

ZRHM-REXA-08-US Spanish CONSENT_PHARMACOGENOMIC for US version 1.0 dated 21-Apr-2014

APPROVED BY
APR 22 2014
MLIRB
Regulatory Information Services Group

**DOCUMENTO DE CONSENTIMIENTO INFORMADO PARA ANÁLISIS GENÉTICO Y FARMACOGENÓMICO**

Título del estudio. Estudio aleatorizado, controlado, abierto, multicéntrico, de 3 grupos paralelos, para demostrar las reducciones en la exposición a constituyentes del humo seleccionados en fumadores aparentemente sanos que cambian al sistema de calentamiento de tabaco mentolado 2.2 (THS 2.2 Menthol) o dejan de fumar, en comparación con continuar usando cigarrillos mentolados convencionales, durante 5 días en internamiento y 86 días más en un contexto ambulatorio.

Protocolo: ZRHM-REXA-08-US

Número de selección del sujeto:	<input type="text"/>
Investigador principal: (Médico del estudio)	Covance Dallas Site Dr. William Lewis
Dirección del centro de investigación:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Número de teléfono:	Covance Dallas Site Tel.: 214-920-9053
Número de teléfono las 24 horas:	Covance Dallas Site Tel.: 972-955-5373
Patrocinador:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Suiza

INTRODUCCIÓN

Usted ya ha aceptado participar en el "Estudio de exposición reducida usando THS 2.2" (el estudio principal), relacionado con el nuevo sistema de calentamiento de tabaco 2.2 (THS 2.2) para la evaluación de los efectos de THS 2.2, un nuevo producto de tabaco de riesgo modificado, sobre los marcadores biológicos (biomarcadores) de exposición seleccionados en comparación con los cigarrillos normales (convencionales).

Este formulario de consentimiento del estudio secundario le informa sobre evaluaciones opcionales que se llevarán a cabo en sujetos que aceptaron participar en el estudio principal. Este formulario de consentimiento informado e información para el sujeto es una adición al

N.º de versión: 3

Aprobado por MLIRB el 04/28/14

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formulario de consentimiento del estudio principal que ya ha firmado. La intención de este documento es ofrecerle información, de forma que pueda decidir si quiere participar en este estudio secundario opcional.

Se le pide que permita la recogida de una muestra de su sangre así como muestras nasales y bucales (de la boca). Se realizarán análisis genéticos con estas muestras. Permitir que se extraigan estas muestras para realizar esta investigación genética es totalmente voluntario. No tiene que aceptar participar en el estudio de investigación genética para participar en el estudio principal.

El médico o el personal del estudio le explicarán todos los procedimientos y responderán cualquier pregunta que pueda tener respecto a este estudio secundario de investigación. Si acepta participar como voluntario, se le pedirá que firme y feche este formulario de consentimiento y se le entregará una copia para que la conserve. Si no acepta participar en el estudio de investigación genética, puede seguir participando en el estudio principal.

Debe haber revisado y firmado el consentimiento informado del estudio principal antes de revisar este formulario de consentimiento.

Este formulario no está pensado para reemplazar al del estudio principal, y el contenido del formulario de consentimiento informado del estudio principal explica el objetivo general de esta investigación y las condiciones de su participación en el estudio principal.

Al firmar este formulario de consentimiento, usted acepta la recogida y el almacenamiento de muestras de sangre, nasales y bucales para realizar análisis farmacogenómicos. La farmacogenómica evalúa el modo en que su estructura genética específica maneja un medicamento.

Este formulario puede contener palabras que usted no comprenda. Pida al médico o al personal del estudio que le expliquen todas las palabras o la información que no entienda con claridad antes de aceptar participar como voluntario en este estudio secundario. Antes de que decida participar, debe entender el objetivo de este estudio secundario opcional, cualquier posible riesgo para usted y lo que se espera de usted durante este estudio secundario. Incluso si acepta participar en este estudio secundario opcional puede cambiar de idea y dejarlo en cualquier momento sin sufrir ninguna penalización ni pérdida de beneficios.

¿QUIÉN ORGANIZA LA INVESTIGACIÓN?

La empresa que patrocina este estudio secundario opcional es Philip Morris Products S.A., Suiza (incluidos agentes, contratistas o consultores). Philip Morris Products S.A. es un fabricante de productos de tabaco. Como se explica en el consentimiento informado del estudio principal, el patrocinador está desarrollando un método alternativo a los cigarrillos convencionales (normales), al desarrollar un producto que puede tener el potencial de reducir algunos de los riesgos de las enfermedades relacionadas con el tabaco.

**CONFIDENCIALIDAD EMPRESARIAL**

La información y cualquier material o artículo que se le entregue sobre o durante el estudio, como información de identificación de la unidad de investigación, el patrocinador y los productos de estudio, y el tipo de estudio que se está realizando, debe considerarse información empresarial confidencial de Covance y el patrocinador del estudio. Por supuesto, tiene la libertad de comentar dicha información de forma confidencial con otros, como su médico o amigos o familiares, con el objetivo de considerar si participar en este estudio o, en cualquier momento, al comentar sus derechos o su atención médica presente o futura. Sin embargo, está prohibida la distribución de información empresarial confidencial, tal como se describe anteriormente, a los medios de comunicación, al igual que su publicación en Internet.

NATURALEZA Y OBJETIVO

Cuando las personas se exponen a sustancias o una mezcla de sustancias (p. ej., alimentos, humo, medicamentos) pueden desencadenarse reacciones en el cuerpo. Estas reacciones o respuestas variarán de una persona a otra, dado que cada persona tiene un material genético (genes) diferente.

Una vez que el organismo absorbe la sustancia, podría afectar al nivel de expresión de estos genes. Estos genes podrían entonces influir en el tiempo que algunas de las sustancias pueden permanecer en el organismo, cómo se descomponen o por qué algunas personas podrían reaccionar de forma diferente a ellas.

Las células son los componentes con los que se construye el cuerpo humano y cada tipo de célula está especialmente adaptada a su función específica en el cuerpo. Todas las células contienen proteínas que se producen a partir de una sustancia llamada ácido ribonucleico mensajero (ARNm) y que permite que las células funcionen.

El objetivo de este estudio secundario es obtener muestras de sangre, nasales y bucales para análisis e investigaciones sobre cómo responderán los fumadores al aerosol (humo) generado por el producto THS 2.2., en comparación con los sujetos expuestos al humo de cigarrillos convencionales, o en comparación con un grupo de sujetos que han dejado de fumar.

La evaluación de estas diferencias puede brindar información sobre los procesos biológicos que se producen al usar el producto del estudio en comparación con el consumo de cigarrillos convencionales o dejar de fumar. También nos permitirá comparar si hay diferencias en el nivel de expresión de estos genes en un fumador entre la boca y la nariz.

Las muestras también se recopilarán para determinar la cantidad y la calidad del ARN (farmacogenómica) en muestras de sangre para comprender si el efecto nocivo de fumar cigarrillos convencionales sobre la función celular podría reducirse al cambiar al producto de prueba o al dejar de fumar.

PROCEDIMIENTOS DEL ESTUDIO

Si acepta participar en este estudio secundario, se le realizarán los tres siguientes procedimientos de recogida de muestras adicionales:

N.º de versión: 3

Aprobado por MLIRB el 04/28/14

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Procedimiento de recogida de muestra epitelial nasal ("recogida de células de la nariz") (Días 0, 6 y 91)

Se le pedirá que se suene la nariz. Este procedimiento se realizará solo en el orificio nasal izquierdo. Si desea que le adormezcan el orificio nasal para el procedimiento, se utilizará un spray anestésico con lidocaína al 1 %. Se introducirá un espéculo nasal (dispositivo parecido a unas pinzas) para ampliar el orificio nasal izquierdo y luego se introducirá un cepillo suave en el orificio nasal y se presionará y girará contra la parte exterior del orificio nasal durante unos 3 segundos, antes de retirarlo. Se introducirá un segundo cepillo suave en el mismo orificio nasal y se presionará y girará contra la parte exterior del orificio nasal durante unos 3 segundos, antes de retirarlo.

Procedimiento de recogida de muestra bucal ("recogida de células de la boca") (Días 0, 6 y 90)

Se le pedirá que se enjuague la boca con agua (unas 4 cucharaditas, 20 ml) que le proporcionaremos. Se introducirá un cepillo estéril en su boca y se presionará ligeramente contra el lateral de su boca (cara interna de la mejilla) hasta que se doble el eje. El cepillo se girará entonces durante unos 10 segundos y se repetirá el procedimiento en la otra mejilla.

Recogida de sangre para transcriptómica (Días 0 y 90)

Se extraerán tres muestras de sangre adicionales para este tipo de análisis (unas 3 cucharaditas, 15 ml en total). Específicamente, se requerirá una muestra de sangre al inicio del estudio en el Día 0, una segunda muestra de sangre en el Día 6 y una tercera muestra al final del estudio en el Día 91.

RIESGOS DE LOS PROCEDIMIENTOS DEL ESTUDIO

Durante la recogida de muestras nasales y bucales, los efectos secundarios que pueden producirse incluyen ardor, dolor, picazón e irritación nasal. En raras ocasiones, puede producirse sangrado de la nariz. Si decide que quiere que le adormezcan los orificios nasales, el spray de lidocaína puede provocar algunas reacciones alérgicas y adormecimiento. Si se utiliza indebidamente, la lidocaína puede provocar efectos secundarios graves como dificultad para respirar, inflamación de la boca o la cara y dolor de pecho.

Durante la recogida de las muestras de sangre, es posible que experimente dolor y/o la formación de moretones en el sitio en que se inserta la aguja/el catéter o en la ubicación del manguito para medir la presión arterial. Aunque es raro, se pueden formar coágulos localizados, producirse daños en los nervios e infecciones. También puede experimentar sensación de desvanecimiento o mareo y/o un desmayo durante la extracción de sangre o poco después.

Los posibles riesgos de la participación en el estudio principal se describen en el documento de consentimiento informado del estudio.

OTROS POSIBLES RIESGOS

Existen posibles riesgos no físicos asociados con esta investigación genética, como los riesgos asociados con una violación de la privacidad o la confidencialidad. La violación de la confidencialidad, puede generar discriminación en las áreas de empleo y seguros, estigmatización social o estrés psicológico provocado por la divulgación de información adversa para usted o su familia. Aunque se supone que estas pruebas son privadas, esto no



se puede garantizar. Por ejemplo, es posible que un tribunal obtenga registros médico o del estudio sin su permiso.

CONFIDENCIALIDAD

Todas sus muestras llevarán un código. Este código contendrá su edad, sexo, raza y otra información. No contendrá su nombre ni sus iniciales. Mientras las muestras se conserven en el centro del estudio principal podrán asociarse con usted. Antes de enviar las muestras fuera del centro del estudio principal a un laboratorio externo para que realice análisis, se anonimizarán. Esto significa que se eliminará la vinculación entre usted y el código de la muestra y no será posible asociar las muestras con usted. La anonimización está prevista para evitar su reidentificación.

Las muestras se enviarán al laboratorio externo para que su análisis después de que se hayan introducido todos los demás datos recopilados durante el estudio principal (aproximadamente 3-4 meses después de que el último voluntario complete el estudio). Como no se pueden vincular con usted las muestras anonimizadas y los datos asociados, no es posible tomar medidas como retirar una muestra, o devolver resultados individuales, aunque nos lo solicite, si la solicitud se hace después de que las muestras se envíen para análisis desde el centro del estudio.

RETIRADA DE LAS MUESTRAS

Como se explicó anteriormente, usted decide libremente si quiere participar en este estudio secundario. Puede dejar de entregar muestras biológicas en cualquier momento. Su decisión de interrumpir su participación en este estudio secundario no afecta a su participación en el estudio principal.

Su médico del estudio principal conservará registros que asocien su información personal con sus muestras codificadas hasta el envío de las muestras a un laboratorio externo para su análisis. Antes de que las muestras abandonen el centro del estudio, se eliminará el vínculo que las asocia con usted. Si retira su consentimiento para el estudio secundario antes de la eliminación de este vínculo, puede solicitar que los investigadores destruyan las muestras y dejen de utilizarse en la investigación. Si retira su consentimiento después de que las muestras abandonen el centro del estudio, no habrá posibilidad de asociarlas con usted y, por tanto, no será posible destruirlas ni excluir esas muestras de análisis futuros.

El patrocinador y los investigadores que trabajan en su nombre tienen derecho a conservar y usar cualquier resultado de investigación que obtengan de las muestras que se recopilaron antes de su retirada del consentimiento.

BENEFICIOS

Puede que no haya un beneficio directo para usted por su participación en este estudio. Sin embargo, su participación puede ayudar a mejorar el conocimiento y la comprensión de enfermedades médicas y el modo en que la gente responde a los productos del estudio. Los investigadores no se comunicarán con usted ni con el médico del estudio en relación con la investigación ni con ninguna información sobre los resultados de las pruebas realizadas en las muestras de este estudio secundario.

ALTERNATIVA

Usted tiene la opción de no participar en este estudio secundario opcional.

N.º de versión: 3

Aprobado por MLIRB el 04/28/14

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**COMPENSACIÓN POR PARTICIPAR EN ESTE ESTUDIO**

La compensación total por este estudio secundario opcional será de \$150.

DESARROLLO DE GANANCIA COMERCIAL

Aunque la investigación futura que use sus muestras puede llevar al desarrollo de nuevos productos, usted no recibirá ninguna compensación por estos nuevos productos. Al aceptar esta investigación, usted renuncia a reclamar cualquier dinero obtenido por los investigadores como consecuencia del uso comercial o de otro tipo de estas muestras.

¿QUIÉN HA REVISADO EL ESTUDIO?

El Comité de Revisión Independiente MLIRB ha revisado los objetivos y la realización prevista del estudio principal.

EN CASO DE LESIONES

Su seguridad es la principal preocupación de todos los miembros del personal del estudio. Comuníquese con el personal del estudio lo antes posible si tiene algún efecto secundario o lesión. Su número de teléfono es 214-920-9053.

El personal del estudio brindará tratamiento médico inmediato, sin costo para usted, para efectos secundarios o lesiones provocados por participar en este estudio. Al margen de los costos del tratamiento médico inmediato, los gastos médicos de cualquier lesión relacionada con la investigación serán responsabilidad de usted o de su tercero pagador, aunque esto no le impide buscar una compensación por una lesión relacionada con una negligencia, falla o culpa por parte de las personas implicadas en la investigación.

PERSONAS QUE DEBEN CONTACTARSE PARA PREGUNTAS, PREOCUPACIONES O QUEJAS

Si tiene alguna pregunta o algún problema, si cree que puede haber sufrido una lesión relacionada con la investigación, o si tiene preguntas sobre la disponibilidad de atención médica, debe comunicarse con el Dr. William Lewis llamando al 214-920-9053.

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Tiene derecho a realizar preguntas en cualquier momento sobre los posibles riesgos o riesgos conocidos de este estudio. Si tiene alguna pregunta relativa a su participación en este estudio, o si en cualquier momento siente que ha experimentado una lesión relacionada con la investigación o una reacción al medicamento del estudio, comuníquese con el Dr. William Lewis llamando al 214-920-9053.

**DERECHOS LEGALES**

Al firmar este formulario de consentimiento, usted no perderá ninguno de los derechos legales a los que de otro modo tiene derecho.

CONSENTIMIENTO Y FIRMAS**Lea el siguiente párrafo en alto a la persona que obtiene el consentimiento.**

He leído la información anterior en un idioma que entiendo bien. Se me ha explicado el contenido y el significado de esta información.

Se me ha ofrecido la oportunidad de realizar preguntas en privado, así como de reunirme con el médico del estudio para comentar este estudio.

He realizado al personal todas las preguntas que tenía y he tenido suficiente tiempo para decidir si deseo participar en este estudio secundario.

Por el presente, acepto voluntariamente y me ofrezco a participar en este estudio y autorizo el uso y la divulgación de mi información médica.

Dono libre y voluntariamente todas y cada una de las muestras biológicas para la investigación que se describen anteriormente y, por el presente, renuncio a todo derecho de propiedad, título e interés que pueda tener sobre esas muestras.

Nombre del participante en letra
de imprenta

Firma del participante

Fecha

Hora

Nombre de la persona que obtiene
el consentimiento informado y la
verificación de que el sujeto sabe leer
en letra de imprenta

Firma de la persona que obtiene el
el consentimiento informado y la
verificación de que el sujeto sabe leer

Fecha

Hora

Recibiré una copia de este formulario de consentimiento del estudio firmado y fechado para conservarla.

Su firma

Fecha

A completar solo por el personal de Covance:

Control de calidad realizado por _____

Fecha _____

N.º de versión: 3

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APPROVED BY
APR 28 2014
MLIRB
Luisa Rodriguez, MD, PhD



**16.1.3.19.3 INFORMED CONSENT DOCUMENT FOR OPTIONAL LONG TERM STORAGE
(BIO-BANKING) OF URINE, PLASMA AND SERUM SAMPLES**



**DOCUMENTO DE CONSENTIMIENTO INFORMADO PARA ALMACENAMIENTO A
LARGO PLAZO OPCIONAL
(BANCO BIOLÓGICO) DE MUESTRAS DE ORINA, PLASMA Y SUERO**

Título del estudio. Estudio aleatorizado, controlado, abierto, multicéntrico, de 3 grupos paralelos, para demostrar las reducciones en la exposición a constituyentes del humo seleccionados en fumadores aparentemente sanos que cambian al sistema de calentamiento de tabaco mentolado 2.2 (THS 2.2 Menthol) o dejan de fumar, en comparación con continuar usando cigarrillos mentolados convencionales, durante 5 días en internamiento y 86 días más en un contexto ambulatorio.

Protocolo: ZRHM-REXA-08-US

Número de selección del sujeto:	<input type="text"/>
Investigador principal: (médico del estudio)	Covance Dallas Site Dr. William Lewis
Dirección del centro de investigación:	Covance Dallas Site 1341 W. Mockingbird Ln., Ste 400E Dallas, TX 75247
Número de teléfono:	Covance Dallas Site Tel.: 214-920-9053
Número de teléfono las 24 horas:	Covance Dallas Site Tel.: 972-955-5373
Patrocinador:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Suiza

INTRODUCCIÓN

Usted ya ha aceptado participar en el "Estudio de exposición reducida usando THS 2.2" (el estudio principal), relacionado con el nuevo sistema de calentamiento de tabaco 2.2 (THS 2.2) para la evaluación de los efectos de THS 2.2, un nuevo producto de tabaco de riesgo modificado, sobre los marcadores biológicos (biomarcadores) de exposición seleccionados en comparación con los cigarrillos normales (convencionales).

Este consentimiento informado le informa sobre el "Almacenamiento a largo plazo opcional (banco biológico) de muestras de plasma, suero y orina para investigación adicional de los biomarcadores de exposición/marcadores de riesgo" (la investigación opcional) que se

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realizará en los sujetos que ya están participando en el estudio principal. Este formulario de consentimiento informado e información para el sujeto es una adición al formulario de consentimiento informado del estudio principal que ya ha firmado.

El médico o el personal del estudio le explicarán todos los procedimientos y responderán cualquier pregunta que pueda tener respecto a esta parte opcional de la investigación. Si acepta participar como voluntario, se le pedirá que firme y feche este formulario de consentimiento y se le entregará una copia original para que la conserve. Nadie puede obligarle a aceptar este almacenamiento a largo plazo opcional de las muestras de sangre y orina para análisis de los biomarcadores/marcadores de riesgo adicionales. Si no acepta participar en este estudio secundario de investigación genética, puede seguir participando en el estudio principal. Debe haber revisado y firmado el consentimiento informado del estudio principal antes de revisar esta hoja de información del sujeto para la investigación opcional. Este formulario no está pensado para reemplazar al del estudio principal, y el contenido del formulario de consentimiento informado del estudio principal explica el objetivo general de esta investigación y las condiciones de su participación en el estudio principal.

Este formulario puede contener palabras que usted no comprenda. Pida al investigador o al personal del estudio que le expliquen todas las palabras o la información que no entienda con claridad antes de aceptar participar como voluntario en esta investigación opcional.

Antes de que decida participar, debe entender el objetivo de este análisis opcional de los biomarcadores de exposición/marcadores de riesgo, cualquier posible riesgo para usted y lo que se espera de usted durante esta investigación opcional. Incluso si acepta participar en esta investigación opcional puede cambiar de idea y dejarlo en cualquier momento sin sufrir ninguna penalización ni pérdida de beneficios.

¿QUIÉN ORGANIZA Y FINANCIA ESTA INVESTIGACIÓN?

La empresa que patrocina esta evaluación opcional es Philip Morris Products S.A., Suiza (incluidos agentes, contratistas o consultores). Philip Morris Products S.A. es un fabricante de productos de tabaco. Como se explica en el consentimiento informado del estudio principal, el patrocinador está desarrollando un método alternativo a los cigarrillos convencionales (normales), al desarrollar un producto que puede tener el potencial de reducir algunos de los riesgos de las enfermedades relacionadas con el tabaco.

OBJETIVO

La finalidad de este documento es pedirle su consentimiento para la obtención de muestras de sangre y el almacenamiento adicional a largo plazo de las muestras resultantes de plasma y suero (las diferentes fracciones de la sangre) así como para la obtención y el almacenamiento a largo plazo de muestras de orina. Además, este documento de consentimiento informado le pide permiso para usar estas muestras para análisis adicionales de los marcadores biológicos y de los riesgos de usar el producto THS 2.2 en comparación con los cigarrillos adicionales.

Estos análisis no incluirán la realización de pruebas genéticas en sus muestras.

PROCEDIMIENTOS DEL ESTUDIO

Si acepta participar en este estudio secundario, se obtendrá una muestra de sangre los Días 0, 6 y 91 del estudio principal (aproximadamente 10 ml por extracción de sangre, 30 ml en total [2 cucharadas]), y se obtendrá una muestra de orina de la orina del estudio principal,

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que comienza los Días 0, 5 y 90 (10 tubos de orina por punto de evaluación, 30 tubos en total; aproximadamente 300 ml de orina en total).

RIESGOS DE LOS PROCEDIMIENTOS DEL ESTUDIO

Durante la recogida de las muestras de sangre, es posible que experimente dolor y/o la formación de moretones en el sitio en el que se inserta la aguja/el catéter o en la ubicación del manguito para medir la presión arterial. Aunque es raro, se pueden formar coágulos localizados, producirse daños en los nervios e infecciones. También puede experimentar sensación de desvanecimiento o mareo y/o un desmayo durante la extracción de sangre o poco después.

Los posibles riesgos de la participación en el estudio principal se describen en el documento de consentimiento informado del estudio.

BENEFICIOS

Puede que no haya un beneficio directo para usted por su participación en esta investigación opcional. Sin embargo, su participación puede aumentar el conocimiento y la comprensión de por qué las personas reaccionan de forma diferente a los productos que contienen tabaco.

ALTERNATIVA

La alternativa es no participar en este estudio secundario.

ANÁLISIS Y ALMACENAMIENTO DE LAS MUESTRAS

Sus muestras de plasma, suero y orina se enviarán para análisis y almacenamiento a largo plazo a los laboratorios contratados por el patrocinador (Philip Morris Products S.A.) que tienen experiencia en analizar y almacenar dichas muestras.

Las muestras se destruirán cuando se haya alcanzado el tiempo de almacenamiento máximo (5 años para las muestras de plasma y orina, y 2 años para las muestras de orina) o cuando ya no se puedan realizar más análisis (lo que suceda primero). Debería saber que Philip Morris Products S.A. podría no realizar toda la investigación inmediatamente, y que sus muestras pueden estudiarse en cualquier momento antes de ser destruidas.

RETIRADA DE LAS MUESTRAS

Puede detener los análisis adicionales en sus muestras en cualquier momento. Comuníquelo al médico del estudio si ya no quiere estar en este estudio secundario.

Si retira su consentimiento para almacenamiento/análisis adicionales de sus muestras, puede solicitar la destrucción de sus muestras de plasma, suero y orina y que ya no se usen en la investigación. Sin embargo, el patrocinador tendrá derecho a conservar y usar cualquier resultado de investigación obtenido antes de su retirada efectiva del consentimiento.

CONFIDENCIALIDAD

Se han adoptado estrictos procedimientos de privacidad y confidencialidad para esta investigación, con el objetivo de mantener su información segura. Todas las muestras recibirán un código. Este código contendrá su edad, sexo, raza y otra información. Cuando dejen el centro de estudio para análisis, sus muestras de plasma, suero y orina no incluirán su nombre ni ninguna otra información personal que pueda identificarlo. Sin embargo, el

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Investigador o el personal del estudio pueden vincular las muestras con usted usando el código de muestra.

El patrocinador puede usar otros laboratorios, investigadores o terceros comerciales o académicos como sus “agentes” para que lo ayuden en esta investigación. Dichas personas están obligadas a mantener los datos confidenciales.

CONFIDENCIALIDAD EMPRESARIAL

La información y cualquier material o artículo que se le entregue sobre o durante el estudio, como información de identificación de la unidad de investigación, el patrocinador y los productos de estudio, y el tipo de estudio que se está realizando, debe considerarse información empresarial confidencial de Covance y el patrocinador del estudio. Por supuesto, tiene la libertad de comentar dicha información de forma confidencial con otros, como su médico o amigos o familiares, con el objetivo de considerar si participar o no en este estudio o, en cualquier momento, al comentar sus derechos o su atención médica presente o futura. Sin embargo, está prohibida la distribución de información empresarial confidencial, tal como se describe anteriormente, a los medios de comunicación, al igual que su publicación en Internet.

¿QUÉ SUCEDERÁ CON LOS RESULTADOS DE ESTA INVESTIGACIÓN OPCIONAL?

No recibirá ninguna información sobre los resultados de esta investigación de biomarcadores opcional. Tampoco recibirá ninguna información sobre los resultados de la investigación opcional que puedan estar relacionados con su salud personal. Aunque tiene derecho a acceder a la información de sus registros médicos, la información que mantendrá el patrocinador en sus bases de datos y que generará durante el análisis de los biomarcadores de exposición/marcadores de riesgo es para fines de la investigación únicamente. El patrocinador no le devolverá ninguna información del análisis de los biomarcadores de exposición/marcadores de riesgo a usted ni al investigador del estudio principal. La información que surja de la investigación no se incluirá en sus registros médicos. En algún momento, es posible que la información sobre los resultados de esta investigación se publique; sin embargo, a usted no se le notificará dicha publicación. Tampoco se le identificará personalmente en ninguna publicación de este tipo.

DESARROLLO DE GANANCIA COMERCIAL

Aunque la investigación futura que use sus muestras puede llevar al desarrollo de nuevos productos, usted no recibirá ninguna compensación por estos nuevos productos. Al aceptar esta investigación, usted renuncia a reclamar cualquier dinero obtenido por los investigadores como consecuencia del uso comercial o de otro tipo de estas muestras.

No se le pedirá que pague ningún análisis relacionado con esta investigación opcional.

**EN CASO DE LESIONES**

Su seguridad es la principal preocupación de todos los miembros del personal del estudio. Comuníquese con el personal del estudio lo antes posible si tiene algún efecto secundario o lesión. Su número de teléfono es 214-920-9053.

El personal del estudio brindará tratamiento médico inmediato, sin costo para usted, para efectos secundarios o lesiones provocados por participar en este estudio. Al margen de los costos del tratamiento médico inmediato, los gastos médicos de cualquier lesión relacionada con la investigación serán responsabilidad de usted o de su tercero pagador, aunque esto no le impide buscar una compensación por una lesión relacionada con una negligencia, falla o culpa por parte de las personas implicadas en la investigación.

¿QUIÉN HA REVISADO LA INVESTIGACIÓN?

El Comité de Revisión Independiente MidLands ha revisado los objetivos y la realización prevista del estudio principal y de este análisis opcional de los biomarcadores de exposición/marcadores de riesgo, y ha otorgado una opinión favorable de ellos.

COMPENSACIÓN POR PARTICIPAR EN ESTE ESTUDIO

La compensación total por este estudio secundario opcional será de \$100. Recibirá esta compensación junto con la compensación por su participación en el estudio principal.

PERSONAS QUE DEBEN CONTACTARSE PARA PREGUNTAS, PREOCUPACIONES O QUEJAS

Si tiene alguna pregunta o algún problema, si cree que puede haber sufrido una lesión relacionada con la investigación, o si tiene preguntas sobre la disponibilidad de atención médica, debe comunicarse con el Dr. William Lewis llamando al 214-920-9053.

Si tiene preguntas sobre sus derechos, preguntas generales, quejas o preocupaciones sobre esta investigación, o preguntas sobre sus derechos como una persona que participa en este estudio, llame al Comité de Revisión Independiente MidLands (MLIRB) al (913) 385-1414 o al (800) 636-4445. Si, en cualquier momento durante o después de su participación en esta investigación, desea información u ofrecer comentarios sobre su experiencia con la investigación, puede llamar al IRB MidLands al número de teléfono anterior o puede entrar en el sitio web del IRB MidLands en www.mlirb.com y dejarnos sus comentarios. En cualquier caso, no tiene que darnos su nombre si no desea hacerlo.

Tiene derecho a realizar preguntas en cualquier momento sobre los posibles riesgos o los riesgos conocidos de este estudio. Si tiene alguna pregunta relativa a su participación en este estudio, o si en cualquier momento siente que ha experimentado una lesión relacionada con la investigación o una reacción al medicamento del estudio, comuníquese con el Dr. William Lewis llamando al 214-920-9053.

DERECHOS LEGALES

Al firmar este formulario de consentimiento, usted no perderá ninguno de los derechos legales a los que de otro modo tiene derecho.

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**CONSENTIMIENTO Y FIRMAS****Lea el siguiente párrafo en alto a la persona que obtiene el consentimiento.**

He leído la información anterior que está en un idioma que entiendo bien. Se me ha explicado el contenido y el significado de esta información.

Se me ha ofrecido la oportunidad de realizar preguntas en privado, así como de reunirme con el médico del estudio para comentar este estudio.

He realizado al personal todas las preguntas que tenía y he tenido suficiente tiempo para decidir si deseo participar en este estudio secundario.

Por el presente, acepto voluntariamente y me ofrezco a participar en este estudio y autorizo el uso y la divulgación de mi información médica.

Dono libre y voluntariamente todas y cada una de las muestras biológicas para la investigación que se describe anteriormente y, por el presente, renuncio a todo derecho de propiedad, título e interés que pueda tener sobre esas muestras.

Nombre del participante en letra
de imprenta

Firma del participante

Fecha

Hora

Nombre de la persona que obtiene
el consentimiento informado y la
verificación de que el sujeto sabe leer
en letra de imprenta

Firma de la persona que obtiene el
consentimiento informado y la
verificación de que el sujeto sabe leer

Fecha

Hora

Recibiré una copia de este formulario de consentimiento del estudio firmado y fechado para conservarla.

Su firma

Fecha

A completar únicamente por el personal de Covance:

Control de calidad realizado por _____

Fecha _____

APPROVED BY
APR 22 2014
MLIRB
Method, Independent Review Board

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