PMI RESEARCH & DEVELOPMENT

Study ZRHM-PK-05-JP
Clinical Study Report Appendix 16.1.3
List of IRBs, IRB Approvals, Sample Consent Forms, and Written Subject Information

Study Title:	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum
Short Title:	Nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Number:	ZRHM-PK-05-JP
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	01 August 2013
Study Completed (last subject last visit):	16 November 2013
Principal Investigator and Affiliation:	F. Nobuoka, MD Ageo Medical Clinic 3133 Haraichi, Ageo City Saitama 362-0021, Japan
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Sponsor Signatories:	Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist Andrea Donelli, Clinical Scientist Nicola Lama, PhD, Biostatistician Patrick Picavet, MD, Medical Safety Officer
Version:	1.0
Date:	12 May 2015

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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16.1.3.1 IRB INFORMATION

IRB	Investigator	Site Number
IRB of Ageo Medical Clinic 3133, Haraichi, Ageo City, Saitama Tomoaki Shimizu Chairperson: Tomoaki Shimizu	F. Nobuoka, MD.	AGE

16.1.3.2 IRB STUDY SUBMISSION LETTER ENGLISH

Form 3

File Number	
Classifications	■ Clinical Study □Post-marketing Study
	□Medical Products □Medical Devices ■ Other

Date: 26/Jun/2013

Clinical Study Request Form

Dear [Name of Head of Institution]
President of Clinic
Ageo Medical Clinic

Sponsor
(b) (4)

We request the following clinical study.

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-PK-05-JP
Clinical Study Name	■ New Request □Continuing Request		
	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum		
	□ The above-mentioned study name may be utilized in the summary of the IRB meeting record. *In case of utilizing another study name, please enter it in the column below.		
	Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)		
The Number of Subjects	62subjects Example: The target number of prospective subjects shall be stated		
Period of Clinical Study	Jul/2013 - Nov/2013		
Contact	Name: (b) (4) TEL: (b) (4) FAX: (b) (4) Email: (b) (4)		

List of Attached Documents

Name of Documents	Documented Date	Version
■ Protocol		
Clinical Study Protocol (ENG and JPN)	21/Jun/2013	1.0
■IB or Package Insert		
Investigator's Brochure (ENG and JPN)	11/Apr/2013	1.0
□ Sample of CRF *Unnecessary, if its contents are sufficiently understood from Protocol.		
	—	
■ Written Informed Consent Form (S)		
	26/Jun/2013	1.0
■ CV of Principal Investigator		
	4/Jun/2013	
■ Name List of Sub Investigators		
	24/Jun/2013	
■ Documents concerning payments and compensation available to subjects (if any)		
Documents related to payments to subjects	No date	
■ Documents concerning the compensation available to the subjects in the event of study-related health injuries.		
Liability Insurance-Certificate of Insurance	6/May/2013	
■ Documents concerning the procedures of subject recruitment (Advertisement, etc.)		
Request of Cooperation for Clinical Study	No date	
□ Documents related to the safety etc. of subjects		
	mm/dd/yyyy	
■ Others		
Assessment of Cough	2012	

Note)
(Head of Institution ≠ PI): Sponsor will create one copy of the original form of this document with the agreement of PI, and will submit it to the head of institution.
(Head of Institution = PI): Sponsor will create one copy of the original form of this document, and will submit it to the head of institution.

Fagerstrom-Nicotine-Dependence-Test	2012	
Modified Cigarette Evaluation Questionnaire (modified	Jul/2007	
Questionnaire of Smoking Urges brief	Feb/2012	

16.1.3.3 IRB STUDY SUBMISSION LETTER JAPANESE

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16.1.3.4 IRB STUDY APPROVAL LETTER ENGLISH

Form 5

File Number	
Classifications	■Clinical Study □Post-marketing Study
	■Medical Products □Medical Devices

Date: 07/04/2013

IRB Result Notification

Dear [Name of Head of Institution]
President of Clinic
Ageo Medical Clinic

Institutional Review Board
IRB of Ageo Medical Clinic
3133, Haraichi, Ageo City, Saitama
Tomoaki Shimizu

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-PK-05-JP
Original Study Name	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum		
Matters Deliberated (Materials Deliberated)	■Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 06/26/2013) □Continuation/Discontinuation of the Clinical Study □Serious Adverse Event (SAE) (□Report on SAE(copy of Form 12 dated mm/dd/yyyy)) (□Report on Adverse Event (AE) (copy of Form 13 dated mm/dd/yyyy)) (□Report on SAE and Defect(copy of Form 14 dated mm/dd/yyyy)) (□Report on AE and Defect(copy of Form 15 dated mm/dd/yyyy)) □Safety Information, etc. (□Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) (□Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) □Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated mm/dd/yyyy)) □Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated mm/dd/yyyy)) □Continued Deliberation (Report on Performance of the Clinical Study (copy of Form11 dated mm/dd/yyyy)) □Others( )		
Deliberation Type	■IRB Deliberation (Deliberation Date : 07/03/2013) □Rapid Deliberation (End Date of Deliberation : mm/dd/yyyy)		
Deliberation Result	■Approval □Approval after corrections □Reject □Withdrawal of approved matters □Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)
To: Principal Investigator NA (Dr. Name of PI)

Date: 07/04/2013

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Ageo Medical Clinic President of Clinic

Note: (Head of Institution ≠ Principal Investigator)
The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)
The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A" shall be stated in the column of the Principal Investigator.

Form 5

File Number	

Date: 07/04/2013

IRB Attendees List

Name	Occupation, License(s) & Affiliation	Classification of members	Attendance	Remarks
Tomoaki Shimizu	Doctor Department of Medicine, Metabolism & Endocrinology, Department of Internal Medicine	2,3	O	
Masayuki Yamakawa	Doctor Yamakawa Clinic	2,3	O	
Sachiko Kinose	Nurse Meguro Orthopaedics Surgery Internal Medicine	2	O	
Masaru Kimura	Chief of Secretariat	1	O	
Taiji Tanaka	Lawyer Tanaka Taiji Law Firm	2,3	X	
Junichi Yoshizawa	Administrative scrivener Administrative scrivener Yoshizawa Legal Service and Accounting office	2,3	O	
Yuki Nakano	Nutritionist Ageo Medical Clinic	1	O	

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interestes with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

Attendance: Described by signals according to the below-mentioned classifications.

O (Members who attended the meeting and have no involvement in the clinical study concerned)

- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)

X (Members who did not attend the meeting.)

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as ""Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".

16.1.3.5 IRB STUDY APPROVAL LETTER JAPANESE

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16.1.3.6 IRB PROTOCOL AMENDMENT SUBMISSION LETTER ENGLISH

Not applicable.

16.1.3.7 IRB PROTOCOL AMENDMENT SUBMISSION LETTER JAPANESE

Not applicable.

16.1.3.8 IRB PROTOCOL AMENDMENT APPROVAL LETTER ENGLISH

Not applicable.

16.1.3.9 IRB PROTOCOL AMENDMENT APPROVAL LETTER JAPANESE

Not applicable.

16.1.3.10 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 1.0 SUBMISSION LETTER ENGLISH

Form 3

File Number	
Classifications	■ Clinical Study □Post-marketing Study
	□Medical Products □Medical Devices ■ Other

Date: 26/Jun/2013

Clinical Study Request Form

Dear [Name of Head of Institution]
President of Clinic
Ageo Medical Clinic

Sponsor
(b) (4)

We request the following clinical study.

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-PK-05-JP
Clinical Study Name	■ New Request □Continuing Request		
	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum		
	□ The above-mentioned study name may be utilized in the summary of the IRB meeting record. *In case of utilizing another study name, please enter it in the column below.		
	Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)		
The Number of Subjects	62subjects Example: The target number of prospective subjects shall be stated		
Period of Clinical Study	Jul/2013 - Nov/2013		
Contact	Name: (b) (4) TEL(b) (b) (4) FAX: (b) (4) Email:(b) (4)		

List of Attached Documents

Name of Documents	Documented Date	Version
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■IB or Package Insert		
Investigator's Brochure (ENG and JPN)	11/Apr/2013	1.0
□ Sample of CRF *Unnecessary, if its contents are sufficiently understood from Protocol.		
	—	
■ Written Informed Consent Form (S)		
	26/Jun/2013	1.0
■ CV of Principal Investigator		
	4/Jun/2013	
■ Name List of Sub Investigators		
	24/Jun/2013	
■ Documents concerning payments and compensation available to subjects (if any)		
Documents related to payments to subjects	No date	
■ Documents concerning the compensation available to the subjects in the event of study-related health injuries.		
Liability Insurance-Certificate of Insurance	6/May/2013	
■ Documents concerning the procedures of subject recruitment (Advertisement, etc.)		
Request of Cooperation for Clinical Study	No date	
□ Documents related to the safety etc. of subjects		
	mm/dd/yyyy	
■ Others		
Assessment of Cough	2012	

Note)
(Head of Institution ≠ PI): Sponsor will create one copy of the original form of this document with the agreement of PI, and will submit it to the head of institution.
(Head of Institution = PI): Sponsor will create one copy of the original form of this document, and will submit it to the head of institution.

Fagerstrom-Nicotine-Dependence-Test	2012	
Modified Cigarette Evaluation Questionnaire (modified	Jul/2007	
Questionnaire of Smoking Urges brief	Feb/2012	

16.1.3.11 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 1.0 SUBMISSION LETTER JAPANESE

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16.1.3.12 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 1.0 APPROVAL LETTER ENGLISH

Form 5

File Number	
Classifications	■Clinical Study □Post-marketing Study
	■Medical Products □Medical Devices

Date: 07/04/2013

IRB Result Notification

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President of Clinic
Ageo Medical Clinic

Institutional Review Board
IRB of Ageo Medical Clinic
3133, Haraichi, Ageo City, Saitama
Tomoaki Shimizu

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-PK-05-JP
Original Study Name	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum		
Matters Deliberated (Materials Deliberated)	■Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 06/26/2013) □Continuation/Discontinuation of the Clinical Study □Serious Adverse Event (SAE) (□Report on SAE(copy of Form 12 dated mm/dd/yyyy)) (□Report on Adverse Event (AE) (copy of Form 13 dated mm/dd/yyyy)) (□Report on SAE and Defect(copy of Form 14 dated mm/dd/yyyy)) (□Report on AE and Defect(copy of Form 15 dated mm/dd/yyyy)) □Safety Information, etc. (□Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) (□Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) □Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated mm/dd/yyyy)) □Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated mm/dd/yyyy)) □Continued Deliberation (Report on Performance of the Clinical Study (copy of Form11 dated mm/dd/yyyy)) □Others( )		
Deliberation Type	■IRB Deliberation (Deliberation Date : 07/03/2013) □Rapid Deliberation (End Date of Deliberation : mm/dd/yyyy)		
Deliberation Result	■Approval □Approval after corrections □Reject □Withdrawal of approved matters □Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)
To: Principal Investigator NA (Dr. Name of PI)

Date: 07/04/2013

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Ageo Medical Clinic President of Clinic

Note: (Head of Institution ≠ Principal Investigator)
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Form 5

File Number	

Date: 07/04/2013

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Tomoaki Shimizu	Doctor Department of Medicine, Metabolism & Endocrinology, Department of Internal Medicine	2,3	O	
Masayuki Yamakawa	Doctor Yamakawa Clinic	2,3	O	
Sachiko Kinose	Nurse Meguro Orthopaedics Surgery Internal Medicine	2	O	
Masaru Kimura	Chief of Secretariat	1	O	
Taiji Tanaka	Lawyer Tanaka Taiji Law Firm	2,3	X	
Junichi Yoshizawa	Administrative scrivener Administrative scrivener Yoshizawa Legal Service and Accounting office	2,3	O	
Yuki Nakano	Nutritionist Ageo Medical Clinic	1	O	

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interestes with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

Attendance: Described by signals according to the below-mentioned classifications.

O (Members who attended the meeting and have no involvement in the clinical study concerned)

- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)

X (Members who did not attend the meeting.)

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as ""Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".

16.1.3.13 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 1.0 APPROVAL LETTER JAPANESE

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B4: Withheld one page, vendor information

16.1.3.14 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 2.0 SUBMISSION LETTER ENGLISH

Not applicable.

16.1.3.15 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 2.0 SUBMISSION LETTER JAPANESE

Not applicable.

16.1.3.16 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 2.0 APPROVAL LETTER ENGLISH

Not applicable.

16.1.3.17 IRB SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 2.0 APPROVAL LETTER JAPANESE

Not applicable.

16.1.3.18 SUBJECT INFORMATION AND INFORMED CONSENT FORM ENGLISH

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM

Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)

Study Title: A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum

Written Information and Informed Consent Form

This document states all necessary information that is useful for you to understand the contents of this clinical study, which you are going to be participating, as well as your benefit and right. Please decide whether to participate in this study by your own free will after you have sufficiently understood the details of this study. If you have any question of this study, please contact us at any time. You will be able to take some time before your reply and are not expected to give us your answer within today. You can take home this Written Information with you to look into it thoughtfully and let us know your decision at a later date.

1. Introduction

Cigarette smoking causes lung and heart disease and other serious diseases in smokers. 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 cannot give up smoking or decide to continue smoking. To those smokers who are not able or not willing to quit, Philip Morris Product S.A. is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases.

The product developed by Philip Morris Product S.A., and to be assessed in this study, is called Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for menthol conventional cigarettes, which can reach 900°C. The THS 2.2 Menthol product comprises the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Tobacco Stick Holder, the Charger, a Cleaning Tool, a mains power supply, and a USB cable. The Tobacco Heating Device comprises everything in THS 2.2 Menthol except the Menthol Tobacco Stick. 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 Menthol Tobacco Stick. Unlike conventional cigarettes, the Menthol Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

It is thought that by heating tobacco rather than burning it as in a normal cigarette it may be possible to reduce the harmful effects of smoking.

So far, no clinical studies have been conducted with the THS 2.2 Menthol. In previous clinical studies, tests on earlier versions of THS 2.2 Menthol showed no safety concerns. However, by participating to this study, you may experience risks and adverse reactions as described in the section 5, Expected Clinical advantages and risks.

2. Purpose of this study

The purpose of this study is a research to collect data on adult smoker using the newly developed Tobacco Heating System 2.2 Menthol.

The purpose of this clinical study is to compare what the body does with nicotine (pharmacokinetics profile) when a THS 2.2 Menthol is used as compared to conventional menthol cigarettes and nicotine replacement therapy gum (NRT gum) (nicorette®) in smoking Japanese healthy smokers. This study will look at participant's urge to smoke and withdrawal symptoms as well as attempt to gather information on the safety of using the new THS 2.2 Menthol product.

Because this is a research study, the study product will be given to you only during this study and not after the study is over.

This study is not intended to recommend continued smoking.

3. Study procedures

3.1 Information on Test Product

The product to be assessed in this study, is called Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol).

THS 2.2 Menthol comprises the following components: Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable.

Charger:	The function of the Charger (Model 4) is to recharge the Holder after use. It contains a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around, and can itself be recharged from a mains power source.
THS Tobacco Stick Holder (Holder):	The function of the Holder (Model 4.2) is to heat the 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).
THS Menthol Tobacco Stick (Menthol Tobacco Sticks):	The Menthol Tobacco Stick (product code C3 Menthol) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder.

So far, no clinical studies have been conducted with the THS 2.2 Menthol, however, a number of clinical studies have been conducted by Philip Morris International and Philip Morris US from 2004 to 2012 with the previous versions of the device (THS 1.0 and THS 2.1). All these studies showed reductions in exposure to selected smoke constituents in subjects who used the THS 1.0 or THS 2.1, as compared to subjects continuing smoking conventional cigarettes.

Participants must be aware that there are no 'safe' cigarettes. Quitting smoking is the only method of reducing the risk of cancer, or any heart, blood vessels and lung diseases associated with smoking.

3.2 Study Design and Procedures

You will be asked to use only two out of the three following products :

- THS 2.2 Menthol
- Menthol conventional cigarettes
- Nicotine replacement therapy gum 2 mg (nicorette®)

As part of the study design you will be randomized to one of four study sequences (by chance, like flipping a coin). If you are randomized to study sequence 1 you will be required to use the THS 2.2 Menthol during Period 1, and you will be required to smoke your own preferred menthol conventional cigarette in Period 2. If you are randomized to sequence 2, you will be required to smoke your own preferred menthol conventional

cigarette during Period 1, and you will use the THS 2.2 Menthol in Period 2. If you are randomized to sequence 3, you will be required to use the THS 2.2 Menthol during Period 1, and you will use the nicorette® in Period 2. If you are randomized to sequence 4, you will be required to use the nicorette® during Period 1, and you will use the THS 2.2 Menthol in Period 2. In any case, whilst you are staying at this hospital, you will be required to adhere to different schedules of product use (THS 2.2 Menthol, menthol conventional cigarettes, and NRT gum [nicorette®]), and procedures.

There are 3 distinct schedules:

- Day -1 ('ad libitum') –On site, you will be allowed to smoke within the designated smoking times between 06:30 and 23:00 hrs except during the procedures on the request of the site.

- Days 0 and 2 ('Washout days') – On these days you will not be allowed to smoke at all.

- Days 1 and 3 ('single use') – On these days you will only be allowed to use once the product you have been allocated to (THS 2.2 Menthol, or menthol conventional cigarette, or nicorette®) in the morning (between 6:00 AM to 9:00 AM). If you are allocated to use the NRT gum, you will chew slowly the nicotine replacement therapy gum for 35±5minutes while spacing each chew as per label. After single use of the product, you will be asked to abstain from nicotine/tobacco-containing items for the rest of the day.

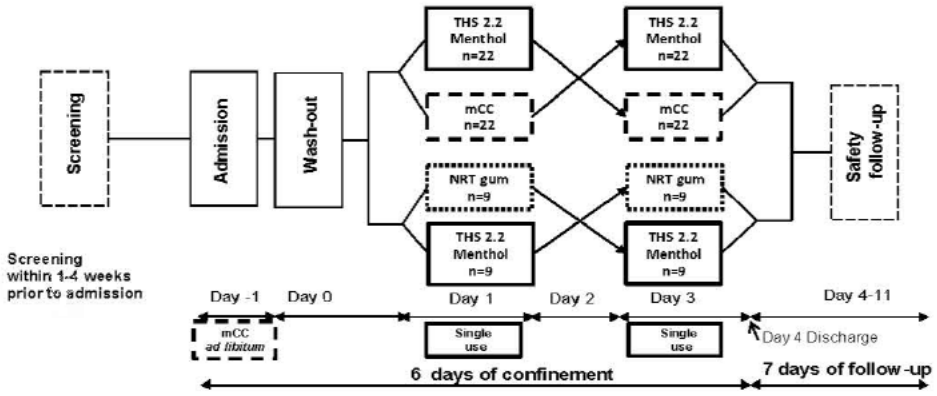
Day 4 - after discharge from this hospital you will be free to smoke your own conventional cigarettes as you wish.

Period 1 consists of Day 0 and Day 1; Period 2 consists of Day 2 and Day 3. As this is a crossover study, on Day 2 each group will crossover i.e. swap. Therefore at the end of the study all participants will have used the THS 2.2 Menthol, only on different days.

The maximum duration of the study from screening until the end of safety follow-up period could be up to 41 days, this includes a screening period of up to 4 weeks prior to admission (Day -29 to Day -2), and 6 days of staying at this hospital (Day -1 to morning of Day 4). In the morning of Day 4, the Day of Discharge examinations will be conducted. You will then enter a 7 day safety follow up until Day 11. During this safety follow-up period you must inform the site of any new medical problem. The site will also contact you to follow-up on any medical problem that has been reported by you during the study but has not been resolved at the time of discharge from this hospital.

Study design of this study is shown in the below figure.

- Cross over with incomplete block design, 4 sequences
- 62 smokers to be randomized



Abbreviations: THS: Tobacco Heating System; mCC = menthol conventional cigarette; NRT = Nicotine Replacement Therapy

Screening Period（Day -29 to Day -2）:

During the Screening Visit, all required test will be performed to assess if you can be considered for this study. If you have satisfactorily fulfilled all of the eligibility criteria you will be invited for the admission day to the study ward on the day before Day -1.. In addition, a demonstration of the THS 2.2 Menthol product and the nicotine replacement therapy gum will also be done by the site staff.

Women can only take part in this study after a negative urine pregnancy test.

Admission (Day -1):

You will be in a confinement setting for 6 days from Day -1 onwards (as examinations start at 6:30 on Day -1, you will be asked to admit to the site the day before).

On Day -1, smoking will not be allowed prior to collection of blood samples to measure Cytochrome P450 2A6 activity and lung function test. Then it will be allowed throughout

the day except during the procedures until 11:00 PM. You will be allowed to continue smoking ad libitum your preferred menthol conventional cigarettes.

Some of the eligibility criteria will be checked again. As the last procedures of the eligibility procedures, you will undergo a THS 2.2 Menthol test first (using up to 3 Menthol Tobacco Sticks) and subsequently nicotine replacement therapy gum test at Day -1 prior to enrolment (except if you are a female and had a positive pregnancy test at Screening or Admission). The nicotine replacement therapy gum will be chewed slowly for 35 ± 5 minutes while spacing each chew as per label. Only if your confirm you are ready, able and willing to use the THS 2.2 Menthol and the nicotine replacement therapy gum during the study you can be considered for enrolment into the study.

You will be enrolled and further randomized to 1 of the 4 study sequences shown below.

	Day 1 (single use)	Day 3 (single use)
Sequence 1 (22 subjects)	THS 2.2 Menthol	Menthol conventional cigarettes
Sequence 2 (22 subjects)	Menthol conventional cigarettes	THS 2.2 Menthol
Sequence 3 (9 subjects)	THS 2.2 Menthol	Nicotine replacement therapy gum (nicorette®)
Sequence 4 (9 subjects)	Nicotine replacement therapy gum (nicorette®)	THS 2.2 Menthol

In total, 62 eligible, smoking subjects will be randomized (by chance like flipping a coin) into 1 of these 4 study sequences.

- **Smoking Restrictions**

You will be eligible into this study only if:

You are aged between 23 and 65 years old and are a smoker of menthol, commercially available and manufactured conventional cigarettes with a maximum of 1 mg nicotine per cigarette, as labeled on the package. You have smoked at least 10 commercially available menthol conventional cigarette per day (no brand restrictions) for the last 4 weeks, you do not plan to quit smoking in the next 3 months, you are ready to accept interruptions of smoking for up to 4 days and you are ready to accept using the THS 2.2 Menthol and the NRT gum product as described in this document.

On Day 1 and Day 3, to avoid cross contamination by second hand smoke, users of THS 2.2 Menthol and smokers of menthol conventional cigarettes will smoke in dedicated separate smoking rooms. You will be asked to smoke alone with an interval between subjects allowing ventilation of the room. Users of nicotine replacement therapy gum will not have access to these rooms.

On Day -1, smoking is only allowed during the designated smoking times from 6:30 AM to 11:00 PM. However, smoking will not be allowed prior to collection of blood samples to measure Cytochrome P450 2A6 activity and lung function test. You will not have free access to your nicotine replacement therapy gum, menthol conventional cigarettes or THS 2.2 Menthol, which will be dispensed by the site staff individually. Smoking is not allowed during study procedures. In addition, smoking is not allowed on Day 4 until all laboratory tests and the test to assess your lung function have been conducted.

During the days of no-smoking (wash-out) or single product use (menthol conventional cigarettes / THS 2.2 Menthol / NRT gum), no nicotine replacement therapy gum or other products supportive to quitting smoking must be used or will be provided to you (e.g. nicotine patches).

If you are willing to make a quit attempt during the study you will be encouraged to do so at any time and you will be given adequate support from the site staff. You can quit smoking at any time during the course of the study.

- **Dietary Restrictions**

A standard diet (in which caloric and fat content is controlled to avoid high-fat diet) will be designed by a dietician for the whole confinement period. You will not be allowed to bring your own food or beverages to this hospital. Meals will be served according to specific schedules provided for this study. Additional light snacks, fruits, and raw vegetables will be available to you. Consumption of water is allowed as desired. The same menu and meal schedule will be administered uniformly for all participants in all study arms. Fasting state has to be observed at least 10 hours prior to blood tests for the safety laboratory on the Screening Visit, on Day -1 and Day 4.

- **Concomitant Medication**

No medication must be taken during the study without prior consultation of the Investigator. The Investigator is responsible for your medical care during your participation in this study. Any decisions regarding the prescription of medication will be taken in your best interest.

- **Check-in procedures**

Investigational site staff will check your identification, check your luggage for prohibited items, ask you questions about your health and the pre-study restrictions and complete an orientation session about the rules and guidelines of the clinic. You should bring enough personal items (underwear, slippers, toiletries, etc.) for your stay.

You should not bring any nicotine replacement products, food, drinks, sweets, chocolate, alcohol, valuables, medicines or large amounts of money.

3.3 Expected duration of your participation

The entire study duration: 14 to 41 days

- Screening period: 1 to 28 days
- Confinement period: 6 days
- Safety follow-up period: 7 days

3.4 Withdrawal from the study / Termination of participation

You are free to withdraw from study (stop your participation) at any time without any penalty. If you want to withdraw from the study, please inform Investigator of your withdrawal at any time. You will be questioned for the reason of premature withdrawal, although you are not obliged to disclose it.

In addition, you will be withdrawn from the study for any of the following reasons:

- The Investigator thinks your safety would be affected by continuing with the study.

- You became pregnant.
- The Sponsor or Investigator decided to stop the study.
- Your withdrawal is considered to be in the best interest of you or the other subjects.

You may also be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Concomitant treatment with non-authorized medication as defined in the context of this study.
- You used any conventional cigarettes or nicotine/tobacco-containing product other than the product/regimen you are assigned to.
- Non-compliance to the study procedures.

3.5 Schedule of events

3.5.1 Screening Visit

The screening Visit will be performed within 4 weeks (Day -29 to Day -2) prior to admission (Day -1). You have to attend this hospital in at least 10-hour fasting state for some clinical laboratory tests to be assessed. First, the participant information and informed consent form (ICF) should be given to you. Only after the ICF signed and dated by you and by the person who conducted the informed consent discussion, the other screening procedures can be performed in the order deemed most practical. It is permissible to complete those over more than one day.

The following assessments will be performed during the screening visits (each procedure other than informed consent may not be conducted in following order):

- ICF to be signed.
- Advice on the risk of smoking / smoking cessation advice and debriefing on THS 2.2 Menthol (you will be explained that THS 2.2. Menthol is not yet demonstrated to be less harmful).
- Demographic data collected (gender, date of birth/age, etc.).
- Identification of current menthol conventional cigarettes brand (brand details will be recorded).

- Medical history/concomitant disease.
- Prior / concomitant medication (you took within 4 weeks of Screening Visit / now taking).
- Smoking history.
- Willingness to quit smoking within the next 3 months (you will be asked if you are planning on stopping smoking in the next 3 months).
- Readiness to abstain from smoking for up to 4 days (you will be asked if you can abstain from smoking for up to 4 days).
- Vital signs assessment (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Blood and urine tests (including hematology, clinical chemistry, laboratory tests, serology for human immunodeficiency virus (HIV) and Hepatitis B and C, urine pregnancy test for females, and urine drug and cotinine screen test).
- Physical examination, height, body weight, including calculation of Body Mass Index (BMI).
- THS 2.2 Menthol and nicotine replacement therapy gum product demonstration by the study site staff.
- Chest X-ray (frontal and left lateral views will be taken: if not performed 6 months prior to Screening Visit).
- Alcohol breath test (using an alcometer device).
- A questionnaire for nicotine dependence.
- Lung function test (has to be done at least 1 hour after smoking):: this will be done first without bronchodilator (salbutamol) inhalation and then with it. 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.
- Electrocardiogram (at least 10 minutes in supine position prior to recording, a painless tracing of your heart rate and rhythm).
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events

3.5.2 Admission (Day -1)

The following assessments will be performed at admission (Day -1):

- Advice on the risk of smoking/smoking cessation advice and debriefing on THS 2.2 Menthol (you will be explained that THS 2.2. Menthol is not yet demonstrated to be less harmful).
- Smoking history.
- Willingness to abstain from smoking for up to 4 days (you will be asked if you can abstain from smoking for up to 4 days).
- Collection of blood samples (including the samples for laboratory tests - to be taken after at least 10 hours of fasting; samples to measure CytochromeP450 2A6 activity –has to be done prior to smoking).
- Urine test (including laboratory tests, urine pregnancy test for females, and urine drug and cotinine screen test).
- Alcohol breath test (using an alcometer device).
- Carbon monoxide breath test (measurement of the carbon monoxide level in your breath).
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Physical examination, weight, Body Mass Index (BMI).
- Identification of current menthol conventional cigarettes brand.
- Lung function test without bronchodilator (has to be done prior to smoking)
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events and concomitant medications.
- Trial of THS 2.2 Menthol product (up to three Tobacco Sticks) and subsequently nicotine replacement therapy gum test.

3.5.3 Investigational period (Day 0 to Day 3):

- <u>Washout (Day of smoking abstinence: Day 0 and Day 2):</u>

You cannot smoke during the washout.

On the days of Washout (Day 0 and Day 2) the following assessments will be performed:

- You will be asked to complete an assessment of cough questionnaire.
- Carbon monoxide breath tests (Measurement of the carbon monoxide level in your breath).
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).

- Blood sampling for nicotine blood levels on Day 2 only.
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events and concomitant medications.

- Days of single use of products (Day 1 and Day 3):

On the days of single use of products (Day 1 and Day 3), you will be asked to use the product you have been allocated to only once in the morning between 6:00 AM to 9:00 AM, and will be asked to abstain from the product or other nicotine/tobacco-containing items for the rest of the day.

On the days of single use of products (Day 1 and Day 3) the following assessments will be performed:

- You will be asked to complete some questionnaires (including assessment of cough, cravings, withdrawal symptoms and product evaluation).
- Blood sampling (including nicotine blood levels and blood samples to measure how much carbon monoxide is bound to your hemoglobin (part of your red blood cells), a total of 42 blood samples will be collected during 2 days).
- Carbon monoxide breath test (Measurement of the carbon monoxide level in your breath).
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Electrocardiogram (at least 10 minutes in supine position prior to recording).
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events and concomitant medications.

3.5.4 Day of Discharge (Day 4)

On the Day of Discharge (Day 4), smoking will be allowed after all laboratory procedures and the lung function test have been performed.

Discharge visit assessments will be performed on Day 4 and will include:

- Advice on the risk of smoking/smoking cessation advice and debriefing on Menthol THS 2.2
- You will be asked to complete an assessment of cough questionnaire.
- Carbon monoxide breath test (Measurement of the carbon monoxide level in your breath).
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement).
- Physical examination and weight, including calculated body mass index.
- Lung function test without bronchodilator (has to be done prior to smoking)
- Blood and urine tests (including hematology, clinical chemistry, laboratory test, blood sampling for nicotine blood levels (1 sample), and urine pregnancy test for females).
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events and concomitant medications.
- Discharge.

3.5.5 Safety Follow-up Period

After you have completed the assessments at Day 4 (or if you have been prematurely withdrawn from the study), you will enter a 7-day safety follow-up period after the time of Discharge. If you experienced the product trial of THS 2.2 Menthol on the admission day and did not participated in the study, or discontinued study participation earlier than Day 4, you will be ask to complete the Day of Discharge assessments shown in the above section of “Discharge Day 4”, and will enter into the follow-up period.

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 problems that has been reported by you during the study but have not been resolved on discharge from the site.

3.5.6 Early Termination

In case of early termination, procedures written in section 3.5.4 “Day of Discharge (Day 4)” will be performed.

3.5.7 Smoking Cessation Advice

You will be given advice on the risks of smoking/smoking cessation advice three times during the study: at the screening visit, at admission (Day -1), and at discharge (Day 4).

TABLE OF STUDY PROCEDURES

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge	Safety follow-up
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Informed consent	●							
Randomisation			●					
Product use				●		●		
Support during periods of reduced smoking/smoking abstinence			●	●	●	●		
Product demonstration of THS 2.2 and NRT gum	●							
Product test for THS 2.2 and NRT gum		●						
Smoking history	●	●						
Readiness to accept interruption from smoking up to 4 days	●	●						
Willingness to quit smoking in the next three months	●							
Advice on risk of smoking and debriefing on THS 2.2	●	●					●	
Demographics , medical history, concomitant diseases	●							
Prior medication / Concomitant medication	●	●	●	●	●	●	●	●
Physical examination, body height, weight and related BMI	●	●					●	
Vital signs	●	●	●	●	●	●	●	
ECG	●			●		●		
Lung function test	●	●					●	
Chest X-ray	●							
Blood and urine analysis	●	●					●	
HIV, Hepatitis B & C blood test	●							
Urine drug and cotinine screen	●	●						
Alcohol breath test	●	●						
Urine pregnancy test (females)	●	●					●	
Plasma nicotine blood test				●	●	●	●	
COHb blood test				●		●		
Carbon monoxide breath test		●	●	●	●	●	●	
CYP2A6 activity (metabolism test)		●						

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge	Safety follow-up
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Subject Questionnaires								
FTND (nicotine dependence)	•							
QSU–brief 'urge to smoke' questionnaire				•		•		
MCEQ (product satisfaction)				•		•		
Cough assessment			•	•	•	•	•	
AE/SAE Recording	•	•	•	•	•	•	•	•

3.6 Sampling Handling and Storage

[Blood collection]

Blood samples will be collected by qualified and trained site personnel. The maximal total volume of blood drawn for each subject will be around 190 ml.

[Urine collection]

Spot urine samples will be taken for urine drug screen, cotinine screen, pregnancy tests and safety urinalysis.

4. Subjects of this study

After you have received sufficient explanation about the study and have given the written consent for participation of the study, the followings will be assessed to confirm your eligibility in the study.

4.1 Who can participate in the study?

- Subject who has signed the ICF and is able to understand the information provided in the Subject Information Sheet and ICF.
- Subject is aged from 23 to 65 years (inclusive).
- Subject is Japanese.

- Smoking, healthy subject as judged by the Investigator based on all available assessments in the Screening period/day of Admission (e.g., safety laboratory, lung function test, vital signs, physical examination, electrocardiogram, chest X-ray, and medical history).
- Subject smokes at least 10 commercially available menthol conventional cigarettes per day (no brand restrictions) with a maximum yield of 1 mg nicotine, as labeled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject has been smoking for at least the last three consecutive years.
- The subject does not plan to quit smoking in the next 3 months.
- The subject is ready to accept interruptions of smoking for up to 4 days.
- The subject is ready to accept using the THS 2.2 Menthol and Nicotine replacement therapy gum.

4.2 Who can not participate in the study?

- As per Investigator judgment, the subject cannot participate in the study for any clinically significant medical reason (e.g. subjects with chronic pulmonary obstructive disease or heart attack in history) or any other reason (e.g. psychiatric and/or social reason).
- A subject who is legally incompetent, physically or mentally incapable of giving consent.
- The subject has a body mass index (BMI) <18.5 or ≥32 kg/m^2.
- The subject has used nicotine containing products other than commercially available conventional cigarettes (either tobacco-based products or nicotine replacement therapy) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
- The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half lives of the drug (whichever is longer) prior to the Admission Day (Day -1), which has an impact on Cytochrome P450 2A6 activity.
- If a subject has received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -1), it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives or subject's safety.
- The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in the study.
- The subject has a positive urine drug test.
- Positive serology test for human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C (smoking under this study may pose a significant risk to these individuals).
- Donation or receipt of whole blood or blood products within 3 months prior to Admission.
- The subject is a current or former employee of the tobacco industry or of their relatives (parent, sibling, child).

- The subject is an employee of this hospital or any other parties involved in the study or of their relatives (parent, sibling, child).
- The subject has participated in a clinical study within 3 months prior to the Screening Visit.
- The subject has previously participated in the same study at a different time.
- Subject is pregnant or is breast feeding.
- For women: Subject does not agree to use an acceptable method of effective contraception

5. Expected Clinical advantages and risks

5.1 Anticipated Benefits

In Japan, research conducted by the Ministry of Health, Labour and Welfare has shown that 35.9% of male and 43.6% of female respondents over 20 years of age expressed the wish to quit smoking. In a large follow-up study of middle aged Japanese smokers, the predictors of smoking cessation were age, job, smoking habit, physical activity, health checkup participation, and health status. Advice on health risks associated with smoking and smoking cessation advice will be provided at Screening, at Admission, and at the Day of Discharge. Subjects who are motivated to quit smoking during the study will be referred to appropriate stop smoking services for continuing support. Subjects who participate in this study will also benefit from repeated, detailed health check-ups, which may help to uncover undiagnosed medical conditions.

5.2 Anticipated Risks and adverse reactions

1) Anticipated Foreseeable Risks due to Investigational Product (THS 2.2 Menthol) and Reference Products (menthol conventional cigarettes / nicotine replacement therapy gum)

- For adverse reactions which THS 2.2/menthol conventional cigarettes Menthol may cause, please refer to “3) Adverse reactions” of this section.
- If you are randomized to receive the nicotine replacement therapy gum you may experience the following side effects: Very common side-effects include runny nose, sneezing, watery eyes, nosebleeds. Common side-effects include headache, dizziness, cough, stomach discomfort, feeling sick, vomiting. Uncommon side-effects include chest palpitations. Abnormal beating of the heart is a very rare side-effect.

- Change in smoking habits (e.g. smoking abstinence) due to study requirements may cause concomitant symptoms including anger, depression, hungriness, anxiety, and difficulty to concentrate which are parts of the craving symptoms.

2) Anticipated Foreseeable Risks due to Study Procedures

- Risks related to blood sampling, e.g. there is a possibility of excessive bleeding, fainting, hematoma, paresthesia, or infection.
- Risks related to chest 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 per X-ray.
- Risks related to drug application as part of testing procedures – for this procedure a short-acting bronchodilator (salbutamol; drug that will “open up” the lungs) will be used. A small risk of an adverse reaction to this drug is possible. Any symptoms you may experience whilst using this drug should be reported to the study doctor immediately.

3) Adverse reactions

Cigarette smoking causes pulmonary and cardiovascular diseases and other serious diseases in smokers. In 2000 in Japan, the proportion of adult deaths due to smoking ranges from 20.0% to 24.9% in males and from 10.0% to 14.6% in females.

Given the current state of knowledge of the THS 2.2 Menthol, at this stage, the harmfulness of THS 2.2 Menthol in terms of tobacco-related diseases is similar to that of Menthol conventional cigarettes.

In the previous clinical study with THS 1.0, a predecessor of THS 2.2 Menthol, an upper extremity deep vein thrombosis (a condition which involves formation of a thrombus [blood clot] in the blood vessel of arm) occurred in a subject who smoked 25 cigarettes per day on average for 20 years, as a serious adverse event possibly related to the study product. The investigator considered that the upper extremity deep vein thrombosis could be related to the travel which involved carrying heavy bag and immobilisation of the subject arms, however, since cigarette smoking is a risk factor of deep vein thrombosis, the investigator concluded that the event is related to the study product. The upper extremity deep vein thrombosis resolved.

A smoker using the THS 2.2 Menthol may experience transient withdrawal symptoms (e.g. urge to smoke, irritability, anxiety feelings, restlessness, and difficulty concentrating) similar to observed during smoking cessation Transient symptoms suggesting mild nicotine intoxication such as stimulant effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, increased ability to concentrate), gastric acid secretion, and vomiting center (nausea, vomiting).

Please correspond with the investigator or site staff in the case of having these or any other abnormal physical condition. Normal treatment is given to these symptoms.

5.3 Unforeseeable Risks

As with any new investigational product, there may be unforeseeable risks and hazards that could occur. Close monitoring and medical supervision are performed to detect any unforeseeable risk or safety signals at the earliest possibility. You will be informed of such risks on screening visit and admission day.

6. Obtaining additional safety information

During the study, we will let you know whenever we get the information for any significant changes of the study, additional information for the risk profile of the product tested, and information which may affect the subject's will. At that time, we will ask you for your intention whether or not you continue to participate in this study.

7. You may withdraw from this study at any time.

You may refuse to take part in this study without any detriment. In addition, you may terminate participation in this study, whenever you want, after you have consented to participate in this study. We guarantee that you will never get any detriment when you quit this study.

8. Protection of Personal Information

Every valuable data of your cooperation and its relevant data for this trail are going to be used for the development of the products. In addition, all those important data might be published at scientific meetings and/or in medical journals. In any cases, we assure you that we will always respect and keep your privacy, and also the hospital officials who are involved in this study and/or its related persons are committed not to disclose such information to outsiders.

In some cases, the study–related persons (e.g. Sponsor's staffs, Institutional Review Board members, and Regulatory Agency staffs) review your medical records as for your treatment (including other departments' records and the duration before the study period). In such cases, these related persons have a duty to respect and keep your private information such as your name.

Signing the Informed Consent Form means that you agreed the direct access to your records. We give our assurance that your test samples such as your blood and/or urine sample will be used only for this study and never used for the other purpose. Then, every analyzed sample will be destroyed after completion of Clinical Study Report.

Additional data analyses not mentioned in the study might be performed with your collected data at a later time. If any additional analyses will be performed, they will fully be covered by data confidentiality, in the same way as the main analyses described in the protocol. By signing the Consent form at the end of this information sheet you are giving your permission for additional analysis of your data for study related purposes.

In order to maintain the confidentiality of the study for the Sponsor you will agree to keep all information relating to the conduct of the study confidential but also you will agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation.

9. In the case of occurrence of Health hazards

The Sponsor is responsible for AEs and health damage of the subjects that are associated with the THS 2.2 Menthol product or with study procedures which are used during this study, except for AEs and health damage of the subjects caused by a negligent or an

intentional misconduct and/or significant deviation to the Protocol of the Investigator or the clinical study site or the subjects. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

10. Fee for conventional cigarettes, Investigational Product and Examination

The cost will be paid by the committed company for this study so that you don't need to pay for THS 2.2 Menthol and Nicotine gum used for this study, while the cost for buying conventional cigarettes will not be paid. The cost for examinations during this study will also be paid by the company.

As for the cost for tests not related to the study procedure, your health insurance and your co-payment would cover those expenses as usual.

11. Compensation for cooperation

When you participate in this clinical study, for your effort and inconvenience for the scheduled visiting and admission, compensation will be offered by the hospital.

12. Duties of the participant

It is the duty of the Participant to conform to the recommendation and requirements of the study, observing the recommendations of the Investigator and the medical personnel of the Site, to observe restrictions resulting from study procedures. Participants staying at the Site must observe the Site Regulations that will be provided to you.

If you have been consulting in the other hospital or other department in the study site, or will consult in the other doctor during the study period, you must contact the investigator (or study collaborator). Information such as your participation in the study and medication(s) to be avoided during the study will be provided to the other doctor(s) by the investigator. The investigator may contact the other doctor(s) and request for information required in the study such as your medical treatment.

You should not take any medication during the study without prior informing the Investigator (or study collaborator). Please correspond with the investigator (or study collaborator) in the case of having abnormal physical condition.

Your responsibilities as a study participant include the following:

- Tell the study doctor about your medical history, current conditions, and any medications you have taken or plan to take.
- Tell the study doctor if you have been in a research study in the last 90 days or are in another research study now.
- If you are a woman who is able to become pregnant, you must practice appropriate methods of birth control or contraception. Your doctor can discuss the method(s) of birth control or contraception that is appropriate for you or acceptable for the study.
- Tell the study doctor about any problems you have during the study.
- Follow the study guidelines as directed by the study doctor and study staff.
- Immediately tell the study staff about any side effects you may have, even those changes you might not consider important.
- Follow instructions and participate in agreed assessments and procedures.

13. Institutional Review Board (IRB) Approval

IRB is a committee, which has been established to assess whether or not the Clinical Study is conducted with respecting the participants' human rights and ensuring their safety, whether it is scientifically/ethically-valid and there is no problem in the Clinical Study Plan. IRB is required to consist of such as medical professionals (medical science and pharmaceutical science), some members other than medical professionals, and also independent members without interest from this Hospital. IRB performs to review the contents of Clinical Study Plan with taking patients' position into careful consideration. The President of our hospital is going to consult IRB members to get opinion concerning the implementation and continuation of the Clinical Study. At the same time, IRB is expected to advise their opinion to our President with reviewing the implementation and continuation of the Clinical Study from the scientific and ethical perspective.

We hereby certify that this Clinical Study has been reviewed and approved by the IRB that is established in Ageo Medical Clinic.

①Name：IRB, Ageo Medical Clinic

②Type of IRB：IRB established in Ageo Medical Clinic

③Founder： President, Ageo Medical Clinic

④Address：3133 Haraichi, Ageo City Saitama, Japan

You are entitled to view Procedure, list of board members, abstract record of this Institutional Review Board. The information is available at the study site. Please feel free to ask the Investigator (or site collaborator) for the information freely.

14. Name, Title and Contact information of Principal and Sub-Investigator

This Clinical Study is conducted by the following Principal Investigator and Sub-Investigator

「Principal Investigator」

Fumimasa Nobuoka M.D.

President

15. Counselling Counter for this study

Please contact us at the following contact information desk if you have any question and/or consultations concerning this Clinical Study.

Information Desk: Clinical Study Office, Ageo Medical Clinic
Contact Person: Tetsu Shimizu
Telephone No: +81-48-723-8011(24 hours)

We ask for your kind understanding concerning this Clinical Study and Investigational product. Please feel free to contact us if you have any question and/or issues need to be explained. After due consideration, please sign the following Informed Consent Form as well as fill in the date of consent with your understanding and agreement for this Clinical Study. Please be sure to receive this Written Information and a copy of Informed Consent Form you signed.

For Hospital (Site)

Informed Consent Form

I have received sufficient explanation and understood the contents of this study, "Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)", therefore, I agree to participate in this study with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy _____

Name (Signature)

Please check

- ☐ I am currently a smoker and have no plan or intent to cease smoking within the next three months.
- ☐ **I am aware that smoking may cause lung cancer, or worsen the risk of myocardial infarction, stroke or aggravation of emphysema, that tobacco smoke could negatively impact people in my vicinity, children and infants or the aged in particular, that I need to exercise caution not to disturb other persons, and that smoking dependency may result from nicotine, although its degree varies from one person to another.**
- ☐ I confirm that I have read and understand the information sheet (Version 1.0, dated 26-June- 2013) for the above study.
- ☐ I confirm that the study has been explained to me and I have had ample time and opportunity to ask questions. I know who to contact if I have any further questions.
- ☐ I understand that relevant sections of my medical notes will be reviewed by representatives of Philip Morris Products S.A., auditors and regulatory authorities where it is relevant to my taking part in the study.
- ☐ I give permission for these individuals to have access to my records.
- ☐ I agree to the transfer of my personal coded data including sensitive data e.g. date of birth, gender to Philip Morris Products S.A. in Switzerland and to regulatory authorities both within and outside Japan and it may be sent to countries that do not have the same level of data protection as Japan.
- ☐ I agree that my personal coded data can be archived.
- ☐ I agree that my biological materials (blood, urine, etc) collected from me can be used for the purposes of this study.
- ☐ I agree to my General Practitioner (GP) being informed that I am taking part in this study. I agree that my GP can give in confidence details of my relevant medical or drug history to the Investigator. I agree that the Investigator can send any health results or medical history obtained during this study to my GP.
- ☐ I agree to the retention of any data collected for a defined period after the point of study completion or my early withdrawal.
- ☐ I agree to keep confidential all information relating to the study product (THS 2.2), including the product design, specifications and method of operation.
- ☐ I agree to take part in this study. At the same time I know that at any time I may cease smoking or withdraw from further participation in this study, without providing a reason.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

Ageo Medical Clinic	_____	_____
Hospital	Department	Title

_____

Principal (Sub) Investigator Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy

Ageo Medical Clinic	_____	_____
Hospital	Department	Title

_____

Seal

For participants

Informed Consent Form

I have received sufficient explanation and understood the contents of this study, "Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)", therefore, I agree to participate in this study with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy _____

Name (Signature)

Please check

- ☐ I am currently a smoker and have no plan or intent to cease smoking within the next three months.
- ☐ **I am aware that smoking may cause lung cancer, or worsen the risk of myocardial infarction, stroke or aggravation of emphysema, that tobacco smoke could negatively impact people in my vicinity, children and infants or the aged in particular, that I need to exercise caution not to disturb other persons, and that smoking dependency may result from nicotine, although its degree varies from one person to another.**
- ☐ I confirm that I have read and understand the information sheet (Version 1.0, dated 26-June- 2013) for the above study.
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I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy Ageo Medical Clinic _____ _____
Hospital Department Title

_____
Principal (Sub) Investigator Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy Ageo Medical Clinic _____ _____
Hospital Department Title

_____
Seal

16.1.3.19 SUBJECT INFORMATION AND INFORMED CONSENT FORM JAPANESE

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