



PMI RESEARCH & DEVELOPMENT

Study ZRHR-REXC-03-EU **Clinical Study Report Appendix 16.1.3** **List of IECs, IEC Approvals, Sample Informed Consent** **Forms, and Written Subject Information**

| | |
|---|---|
| Study Title: | A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement |
| Study Number: | ZRHR-REXC-03-EU |
| Product Name: | Tobacco Heating System 2.2 (THS 2.2) |
| Study Initiated (first subject screened): | 29 June 2013 |
| Study Completed (last subject last visit): | 26 September 2013 |
| Principal Investigator and Affiliation: | Katarzyna Jarus-Dziedzic, MD, PhD BioVirtus Research Site Sp. z o.o., Mokra 7 05-830 Kajetany, Poland |
| 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 Guillaume de La Bourdonnaye, MEng, MSc, Biostatistician Kausar Aamir, MD, PhD, Medical Safety Officer |
| Version: | 2.0 |
| Date: | 08 March 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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**16.1.3.1 IEC INFORMATION**

| IEC | Investigator | Site Number |
|--|-------------------------------------|--------------------|
| Komisja Bioetyczna Przy Okręgowej Izbie Lekarskiej w Warszawie 02-512 Warszawa, ul. Puławska 18 Chairperson: Marek Czarkowski | Dr n. med. Katarzyna Jarus-Dziedzic | BIO |



16.1.3.2 IEC STUDY SUBMISSION LETTER ENGLISH



[logo:] BioVirtus Research Site

Centre for Clinical Trials of Bioequivalence,
Early Phases and Studies Involving Special Patient Populations

COPY

Warsaw, 7 May 2013

**Ethics Committee
at the Regional Medical Chamber in Warsaw
ul. Puławska 18
02-512 Warszawa**

Dear Sir or Madam,

We kindly request your opinion on the conduct of the clinical trial titled:

**“A Randomized, Controlled, Open-label, 3-arm Parallel Group, Single Center Study to
Demonstrate Reductions in Exposure to Selected Smoke Constituents in Smoking,
Healthy Subjects Switching to the THS 2.2 or Smoking Abstinence, Compared to
Continuing to Use Conventional Cigarettes, for 5 Days in Confinement”
(study code: ZRHR-REXC-03-EU)**

PHILIP MORRIS PRODUCTS S.A. is the Study Sponsor.

The Sponsor subcontracted the conduct of this medical experiment to the site of BioVirtus Research Site Sp. z o.o., ul. Mokra 7, 05-830 Kajetany.

Katarzyna Jarus-Dziedzic will act as the Principal Investigator.

Enclosed please find an application along with appendices (the list of appendices can be found in the application).

Should you have any questions, please contact the Applicant, at the site's address:
BioVirtus Research Site Sp. z o.o., ul. Mokra 7, 05-830 Kajetany, phone +48 22 101 07 54,
fax: +48 22 101 07 56, or by e-mail: k.jarus@biovirtus.pl

[stamp:]

Secretary's office of the Ethics Committee
at the Regional Medical Chamber in Warsaw

Date: 2013-05-08

RECEIVED

/illegible signature/

Yours faithfully,
/illegible signature/

President of the Management Board, Chief Medical and Scientific Officer
Katarzyna Jarus-Dziedzic, M.D., Ph.D.



B4: Withheld one page, vendor information



16.1.3.4 IEC STUDY APPROVAL LETTER ENGLISH



16.1.3.3 IEC STUDY SUBMISSION LETTER POLISH

[Logo]
BIOETHICS COMMITTEE
at the District Medical Board in Warsaw

02-512 Warszawa, ul. Puławska 18
tel.: 22 542 83 12, tel/fax: 22 542 83 13

Resolution No. 20/13
of the Bioethics Committee
at the District Medical Board in Warsaw
of 23 May 2013

as regards a medical experiment opinion, register No. KB/891/13

Pursuant to Article 29, Section 1 of the Act of 5 December 1996 on the Professions of Physician and Dentist (Journal of Laws 2008, No. 136, Item 857 as amended), §6 of the Regulation of the Minister of Health and Social Welfare of 11 May 1999 on Particular Guidelines for Appointing, Funding and Operation of Bioethics Committees (Journal of Laws No. 47, Item 480) and the Pharmaceutical Law Act of 6 September 2004 (Journal of Laws 2008, No. 45, Item 271 as amended), it is resolved as follows:

§1

The Bioethics Committee at the District Medical Board in Warsaw composed of the following:

1. Chairperson - Marek Czarkowski, MD, PhD
2. Deputy Elżbieta Przymus - Góralczyk, MS Pharm
3. Andrzej Dąbrowski, MD, PhD
4. Attorney Sławomir Lis
5. Msg. Prof. Stefan Kornas
6. Aleksander Kotlicki, MD, PhD
7. Prof. Magdalena Marczyńska, MD, PhD
8. Stanisław Niemczyk, MD, PhD
9. Renata Piasecka-Krawczyk, MS
10. Joanna Romejko - Jarosińska, MD PhD

at the session on 23 May 2013 issued an approval of the following medical experiment:

Study title: *A randomised, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement.*

Principal Investigator **Dr. Katarzyna Jarus - Dziedzic**

The study will be conducted at the BioVirtus Research Site Sp. z o.o., ul. Mokra 7, 05-830 Kajetany

§2

The Bioethics Committee finds that the application filed contains a complete set of documentation, including in particular:

1. Application of the principal investigator dated 05.08.2013
2. Signed curriculum vitae of the principal investigator in Polish dated 7 May 2013;
3. Information about the site dated 7 May 2013;
4. Patient Information and Informed Consent Form, version 1.0 dated 03 May 2013;
5. Patient Information and Informed Consent Form for the optional transcriptomic study, version 1.0 dated 07 May 2013;
6. Data Processing Patient Consent Master (included in the Informed Consent Form);
7. A copy of the study insurance policy issued by:
8. (b) (4) policy No. (b) (4) of 24 April 2013 (the policy is accompanied by proof of payment of the insurance premium)
9. A copy of the civil liability insurance policy for the Site comprising civil liability insurance of the Investigator and the entire research team (policy No. (b) (4) issued by the insurance and reinsurance company: (b) (4);
10. Protocol synopsis in Polish, final version dated 25 April 2013;
11. Study Protocol, final version dated 25 April 2013;
12. Additional documents to the Protocol: Protocol signature page dated by
13. Katarzyna Jarus-Dziedzic, MD, PhD on 26 April 2013;
14. Investigator's Brochure, version 1.0 edition No. 2 of 11 April 2013;
15. CRF version 0.2 dated 03 May 2013 (printout of the electronic CRF)
16. Framework Agreement for Clinical Services between BioVirtus Research Site Sp. z o.o. and the company COVANCE concluded on 22 April 2013, and its translation;
17. Clinical Study Contract ZRHR-REX-03-EU of 13 May 2013, and its translation.
18. Other patient forms:
 - a. Minnesota Nicotine Withdrawal Scale (MNWS), Polish version dated 24 April 2013;
 - b. Modified Cigarette Evaluation Questionnaire, (mCEQ), Polish version dated 24 April 2013;
 - c. Questionnaire of Smoking Urges (QSU), Polish version dated 24 April 2013;
 - d. HST Questionnaire (topography of smoking), Polish version 0.1 dated 24 April 2013;
 - e. Fagerstrom Nicotine Dependence Test, Polish version dated 24 April 2013;
 - f. Coughing evaluation, Polish version dated 24 April 2013;
 - g. Electronic diary printout, Polish language version 1.0 dated 3 May 2013 (Polish version questionnaires to be completed by participants in the electronic diary can be found in separate documents listed above);
19. Agreement on the Study Sponsor's responsibility for the investigational product (Letter of Agreement) dated 23 April 2013;
20. Consent of the Director of BioVirtus Research Site Sp. z o.o. to perform the study at the Site, dated 07 May 2013;
21. Statement by the Chairman of the Board of the Hearing and Speech Center Medincus (building administrator) concerning cigarette smoking by study participants in designated smoke rooms, dated 25 April 2013;
22. Other materials for the Participants:
 - a. Tobacco heating device (model 2.2) user manual.

(The aforementioned documents have been listed according to the information in the application submitted by the Principal Investigator)

§3

The composition and activities of the Ethics Committee are consistent with the Guidelines and Recommendations for the European Ethics Committees developed by the EFGCP, Good Clinical Practice (GCP) and local requirements.

§4

The resolution shall enter into force on the date it has been passed and is in effect for the term of the insurance policy enclosed with the application.

§5

Bioethics Committee shall require of the Principal Investigator:

1. notification of any changes and deviations from the clinical trial protocol,
2. notification of any new information related to adverse effects on the safety of persons participating in the trial and on its course,
3. notification of any serious or unexpected adverse reactions to the drugs (ADR) and serious adverse events (SAE)
4. to inform about any decisions of other bioethics committees,
5. preparation of annual reports on the progress of the experiment (no later than the end of December of each year)
6. to inform of the end of the experiment and its results, including the requirement to provide a copy of the final version of the experiment report once it ends.

All correspondence must be sent in writing by registered mail or with confirmation of receipt.

§6

The text of the resolution has been drawn up in 2 identical copies, one for the applicant and one for the Bioethics Committee.

§7

Within 14 days of its receipt, the applicant has the right to appeal this resolution to the Appellate Bioethics Committee at the Ministry of Health through the Ethics Committee of the District Medical Chamber in Warsaw.

.....
Signature of the Chairperson

Signatures of the Bioethics Committee members voting project KB/891/13
on 23 May 2013

Principal investigator: Dr.Katarzyna Jarus-Dziedzic

Chairperson

Marek Czarkowski, MD, PhD
(internist, endocrinologist, cardiologist)

[Signature]

Members:

Elzbieta Przymus – Góralczyk, MS Pharm
(Deputy Chairperson, pharmacist)

[Signature]

Associate Prof. Stanisław Ancyparowicz, MD,
PhD (surgeon)

Andrzej Dąbrowski, MD, PhD
(internist, pulmonologist, allergist)

[Signature]

Attorney Sławomir Lis
(legal counsel)

[Signature]

Wanda Kaminska, PhD
(philosopher)

Msg. Prof. Stefan Kornas
(clergyman, ethicist)

[Signature]

Aleksander Kotlicki, MD, PhD
(internist)

[Signature]

Prof. Magdaleną Marczyńska, MD, PhD
(pediatrician)

[Signature]

Ewa Miękus-Pączek, DDS
(dentist)

Prof. Stanisław Niemczyk, MD
(nephrologist, endocrinologist,
clinical transplantologist)

[Signature]

Renata Piasecka-Krawczyk, MS
(nurse)

[Signature]

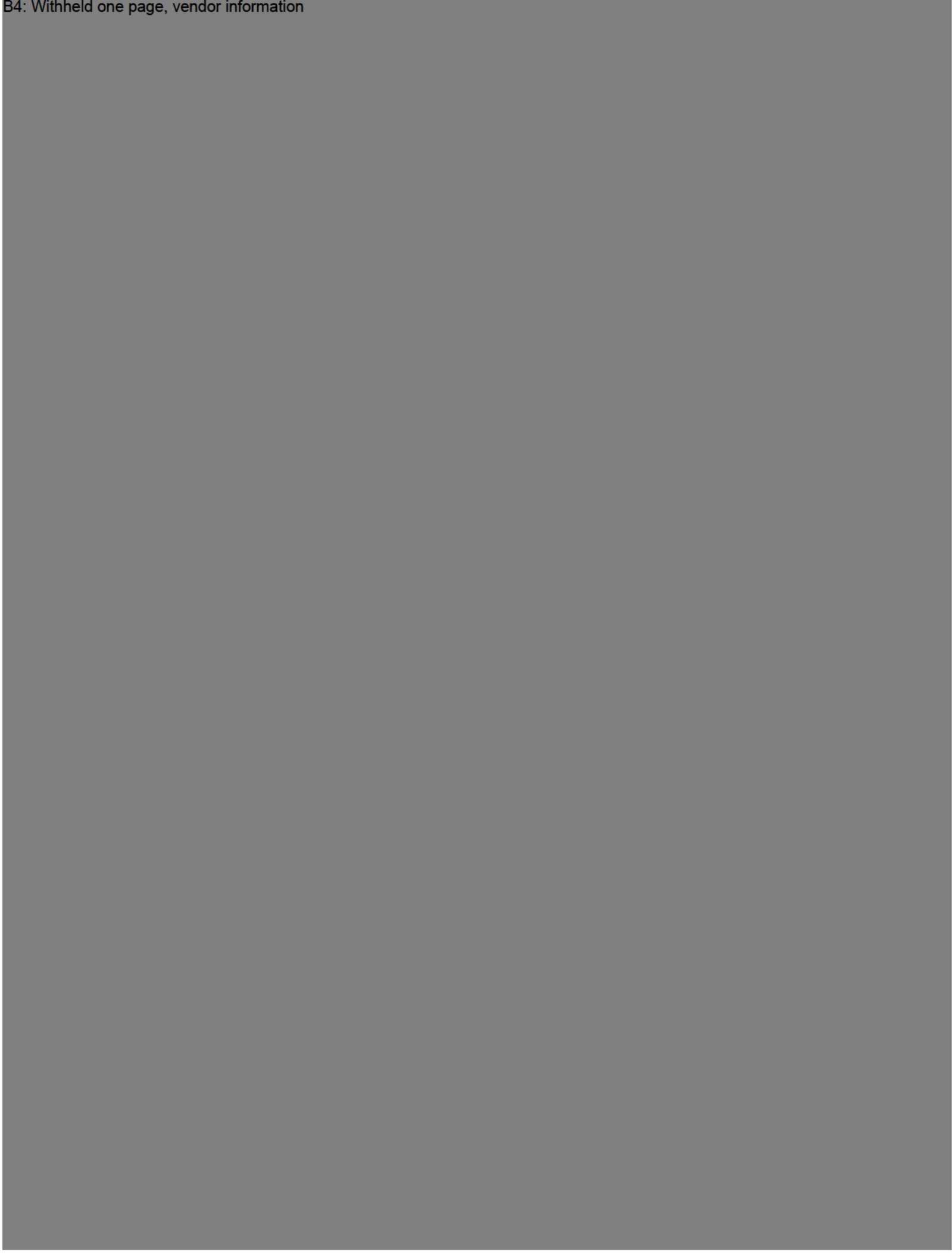
Bożena Pietrzykowska, MD
(psychiatrist)

Joanna Romejko-Jarosińska, MD, PhD
(internist, clinical oncologist)

[Signature]

Marek Stopiński, MD, PhD
(internist, nephrologist)

16.1.3.5 IEC STUDY APPROVAL LETTER POLISH



**16.1.3.6 IEC PROTOCOL AMENDMENT SUBMISSION LETTER
ENGLISH**

Not applicable.

**16.1.3.7 IEC PROTOCOL AMENDMENT SUBMISSION LETTER
POLISH**

Not applicable.

**16.1.3.8 IEC PROTOCOL AMENDMENT APPROVAL LETTER
ENGLISH**

Not applicable.

**16.1.3.9 IEC PROTOCOL AMENDMENT APPROVAL LETTER
POLISH**

Not applicable.



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



PMI RESEARCH & DEVELOPMENT

Philip Morris Products S.A

Clinical Study Report Appendix 16.1.3

Confidential

ZRHR-REXC-03-EU

Version 1.0 / 17 March 2015

Page 23 of 88

[logo:] BioVirtus Research Site

Centre for Clinical Trials of Bioequivalence,
Early Phases and Studies Involving Special Patient Populations

COPY

Warsaw, 7 May 2013

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[stamp:]

Secretary's office of the Ethics Committee
at the Regional Medical Chamber in Warsaw
Date: 2013-05-08

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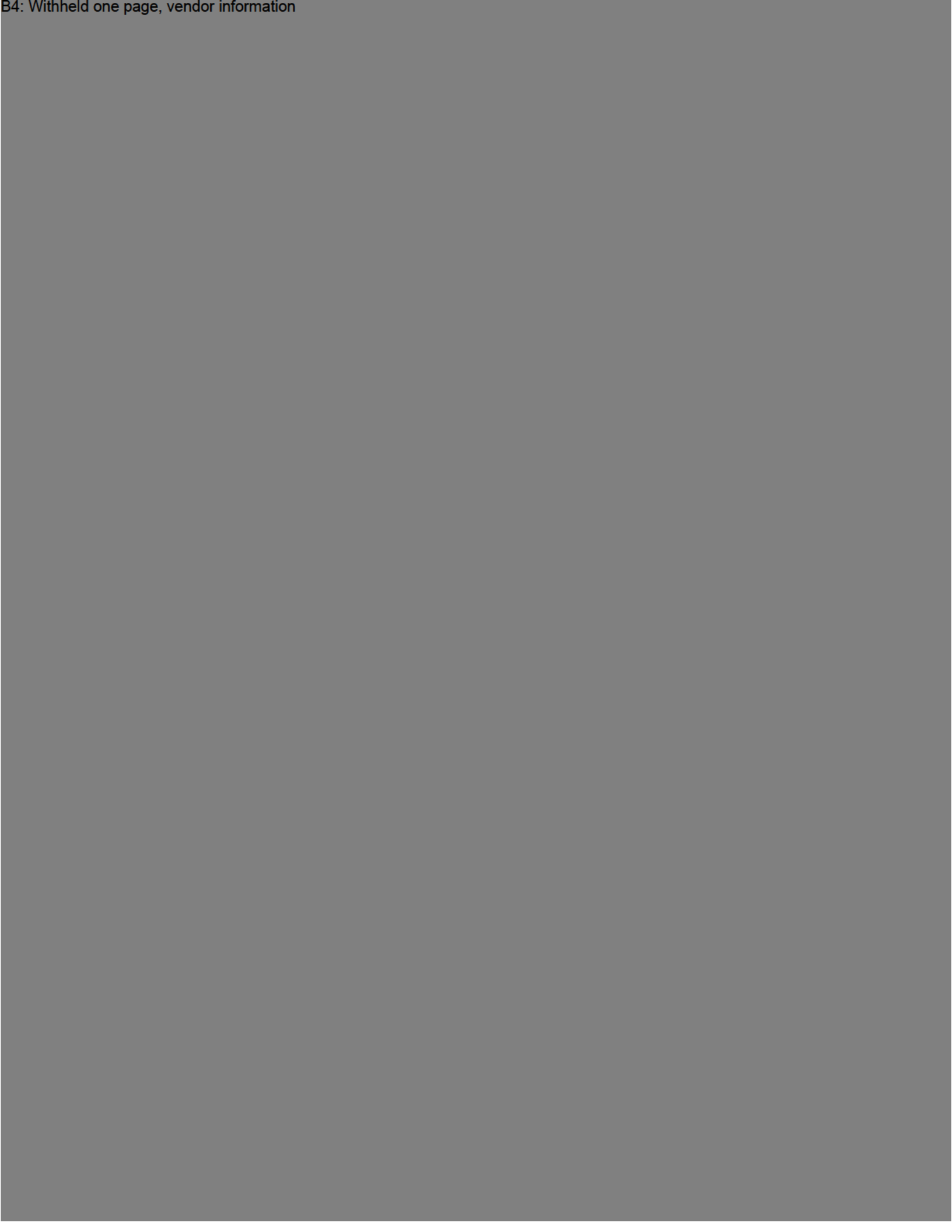
/illegible signature/

Yours faithfully,

/illegible signature/

President of the Management Board, Chief Medical and Scientific Officer
Katarzyna Jarus-Dziedzic, M.D., Ph.D.

**16.1.3.11 IEC SUBJECT INFORMATION AND INFORMED CONSENT
FORM VERSION 1.0 SUBMISSION LETTER POLISH**



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



[Logo]
BIOETHICS COMMITTEE
at the District Medical Board in Warsaw

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7. Prof. Magdalena Marczyńska, MD, PhD
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Principal Investigator

(b) (4)

The study will be conducted at the

(b) (4)



§2

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6. Data Processing Patient Consent Master (included in the Informed Consent Form);
7. A copy of the study insurance policy issued by:
8. AXA Corporate Solutions, policy No. (b) (4) of 24 April 2013 (the policy is accompanied by proof of payment of the insurance premium)
9. A copy of the civil liability insurance policy for the Site comprising civil liability insurance of the Investigator and the entire research team (policy No. (b) (4) issued by the insurance and reinsurance company Towarzystwo Ubezpieczeń i Reasekuracji Allianz Polska S.A., ul. Rodziny Hiszpańskich 1, 02-685 Warsaw);
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11. Study Protocol, final version dated 25 April 2013;
12. Additional documents to the Protocol: Protocol signature page dated by
13. Katarzyna Jarus-Dziedzic, MD, PhD on 26 April 2013;
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 3. notification of any serious or unexpected adverse reactions to the drugs (ADR) and serious adverse events (SAE)
 4. to inform about any decisions of other bioethics committees,
 5. preparation of annual reports on the progress of the experiment (no later than the end of December of each year)
 6. to inform of the end of the experiment and its results, including the requirement to provide a copy of the final version of the experiment report once it ends.
- All correspondence must be sent in writing by registered mail or with confirmation of receipt.

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The text of the resolution has been drawn up in 2 identical copies, one for the applicant and one for the Bioethics Committee.

§7

Within 14 days of its receipt, the applicant has the right to appeal this resolution to the Appellate Bioethics Committee at the Ministry of Health through the Ethics Committee of the District Medical Chamber in Warsaw.

.....
Signature of the Chairperson

Signatures of the Bioethics Committee members voting project KB/891/13
on 23 May 2013

Principal investigator: Dr.Katarzyna Jarus-Dziedzic

ChairpersonMarek Czarkowski, MD, PhD
(internist, endocrinologist, cardiologist)

[Signature]

Members:Elżbieta Przymus – Góralczyk, MS Pharm
(Deputy Chairperson, pharmacist)

[Signature]

Associate Prof. Stanisław Ancyparowicz, MD,
PhD (surgeon)Andrzej Dąbrowski, MD, PhD
(internist, pulmonologist, allergist)

[Signature]

Attorney Sławomir Lis
(legal counsel)

[Signature]

Wanda Kaminska, PhD
(philosopher)Msg. Prof. Stefan Komas
(clergyman, ethicist)

[Signature]

Aleksander Kotlicki, MD, PhD
(internist)

[Signature]

Prof. Magdaleną Marczyńska, MD, PhD
(pediatrician)

[Signature]

Ewa Miękus-Pączek, DDS
(dentist)Prof. Stanisław Niemczyk, MD
(nephrologist, endocrinologist,
clinical transplantologist)

[Signature]

Renata Piasecka-Krawczyk, MS
(nurse)

[Signature]

Bożena Pietrzykowska, MD
(psychiatrist)Joanna Romejko-Jarosńska, MD, PhD
(internist, clinical oncologist)

[Signature]

Marek Stopiński, MD, PhD
(internist, nephrologist)



16.1.3.13 IEC SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 1.0 APPROVAL LETTER POLISH

Not applicable.



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

Not applicable.



16.1.3.15 IEC SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 2.0 SUBMISSION LETTER POLISH

Not applicable.



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

Not applicable.



16.1.3.17 IEC SUBJECT INFORMATION AND INFORMED CONSENT FORM VERSION 2.0 APPROVAL LETTER POLISH

Not applicable.



16.1.3.18 SUBJECT INFORMATION AND INFORMED CONSENT FORM ENGLISH

The following versions of the ICF were used in the study:

Final v1.0 03 May 2013 Main Study

ICF Transcriptomics v1.0 07 May 2013

Subject Screening No.: **SUBJECT INFORMATION AND INFORMED CONSENT FORM****Study: ZRHR-REXC-03-EU**

Principal Investigator: Dr Katarzyna Jarus-Dziedzic MD, PhD

Site: BioVirtus Research Site Sp z o o
Address: Mokra 7, 05-830 Kajetany, Poland
Tel: +48 22 101 07 54
Fax: +48 22 101 07 56

Study Title: A randomised, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement

1. Introduction

You have been invited to participate in an experimental medical study. This document contains information about the purpose and the course of the study, as well as benefits and risks related to your participation. It is important that you understand what the study involves before giving your consent to participate. Please read carefully all the information below. Should you have any questions, please ask the study physician ("Investigator"). You can ask the Investigator about any issue, which is in your opinion, related to the study.

You can take with you a copy of this Informed Consent Document (unsigned), to think it over or discuss with your family or friends before you decide about your participation in this study. Once you signed and dated this Informed Consent Form, in the presence of the Principal Investigator, you will receive one original which you will take home with you.

When making the decision to participate in the study, it is important that you accept its course, its purpose, the planned procedures, and that you are ready to participate until the end of the study.

Covance Inc., 210 Carnegie Center, Princeton, New Jersey 08540-6233, USA ("CRO") have been contracted by Philip Morris Products S.A., Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland (PMP), the company commissioning the conduct of the study ("Sponsor"), to supervise the study conduct. Covance Inc. has contracted BioVirtus Research Site Sp z o o (the "Site") to conduct this study and will cover BioVirtus' costs.

This research study will be carried out according to the ethical principles included in the Helsinki Declaration (2008), the requirements of "International Conference on Harmonisation/Good Clinical Practice" (ICH GCP) (to the extent possible for this research study), and in accordance with Polish law. Before the start of any study which involves the participation of subjects the study Protocol (including detailed information about the study and all procedures) and other relevant documentation are submitted to the Independent Ethics Committee in order to obtain the Committee's opinion in terms of scientific and ethical aspects. The approval of this Committee is necessary to start the study.

2. What is the purpose of this study?

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, PMP is working to offer an alternative approach by developing products with the potential to reduce the risks of tobacco related

Subject Screening No.:

diseases

The main purpose of the study is to evaluate the effect of a new modified risk tobacco product ("MRTP") – Tobacco Heating System 2.2 (THS 2.2) on selected biomarkers of exposure ("BioExp") compared to conventional cigarettes (CC) (The term 'conventional cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, and other nicotine-containing products). Biomarkers of exposure can be described as substances measured in your body as the result of consumption of another substance e.g. you will intake carbon monoxide (CO) when you smoke. Carbon monoxide binds in your body to hemoglobin contained in your red blood cells. The level of CO bound to this haemoglobin will be measured, among others, in this study and is referred to as biomarker of exposure to CO. This study will also look at people's urge to smoke and any withdrawal symptoms; to gather information on the safety of using the new THS 2.2 product.

In addition, some analysis will be conducted in the study to assess human smoking behaviour by way of Human Smoking Topography ("HST") using the HST SODIM® device when using the THS 2.2 product compared to conventional cigarettes. The impact of the HST SODIM® on smoking behaviour will also be assessed.

3. Information on the test product – Tobacco Heating System (THS 2.2) The product developed by PMP and to be assessed in this study, is called THS 2.2. With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for conventional cigarettes, which can reach 900°C. The THS 2.2 product comprises the following components: the THS Tobacco Stick, Holder, the Charger, a Cleaning Tool, a main power supply, and a USB cable. The function of the Holder is to heat the THS Tobacco Stick, delivering an aerosol to the user. The Holder is powered from an internal battery which delivers power for about 6 Minutes (allowing complete use of a single THS Tobacco Stick). Unlike conventional cigarettes, THS Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

So far, no clinical studies have been conducted to evaluate THS 2.2. In previous clinical studies, tests on earlier versions of THS 2.2 showed no safety concerns. However, by participating to this study, you may experience some events as described in the section describing risks.

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.

4. Who can participate in the study?

- Subjects who in the opinion of the Investigator do not show signs of significant disease on the basis of their medical history, physical examination, blood and urine laboratory tests and other tests results (heart actions (ECG), chest X-ray, lung function test (spirometry), vital signs (blood pressure, breathing rate and heart rate));
- Subjects who currently smoke, based on self-reporting, and for the last 4 weeks have smoked at least 10 non-mentholated conventional cigarettes per day. In addition, subjects must have smoked for at least the last three consecutive years and who do not plan to quit smoking in the next 3 months.
- Caucasian men and women, between 21 to 65 years old inclusive.
- Non-pregnant women using a contraceptive method approved in the study Protocol, or post-menopausal women.
- Subjects ready and willing to use exclusively the THS 2.2 product over 5 days, if assigned to this arm of the study.
- Subjects who are ready to accept 5 days of smoking abstinence, if assigned to this arm.
- Subjects whose Body Mass Index (BMI) is greater than 18.5 and less than or equal to 32 kg/m².

Subject Screening No.:

BMI is calculated by dividing body mass (expressed in kilograms) by squared height (expressed in meters)

5. Who cannot participate in the study?

Subjects who:

- In the opinion of the Investigator cannot participate in the study for any medical reason (e.g. subjects with chronic pulmonary obstructive disease or having suffered a heart attack)
- Have used nicotine replacement therapy, or nicotine products other than commercially available conventional cigarettes (including electronic cigarettes), within 4 weeks prior to assessment
- Participated in any other clinical study or medical experiment within the 3 month period prior to screening visit
- Within the 3 month period prior to the planned admission to the site donated blood or received blood or derivative products
- Have taken medication within 14 days of admission, which has an impact on CYP1A2 or CYP2A6 activity (enzymes actively involved in medication metabolism). Examples of types of medications with effect on CYP1A2 and CYP2A6 may include the following: Antibiotics, Antidepressants, Neuroleptic, Antiepileptic, Antihypertensive, Hormonal contraceptives, Cholesterol lowering agents, Analgesic, Anti-diabetic. This list is not exhaustive and all taken medications should be discussed with the Investigator
- Are (or have been) employed in tobacco industry, or their close relatives (parent, sibling, children)
- Work for the Site or any other company involved in this study or their close relatives (parent, sibling, children)
- Have a limited legal capacity in order to give consent
- Have previously participated in the same study at a different time
- Whose liberty has been restricted by force of an administrative or court decision, or who are on probation or;
- Are pregnant or breast-feeding women

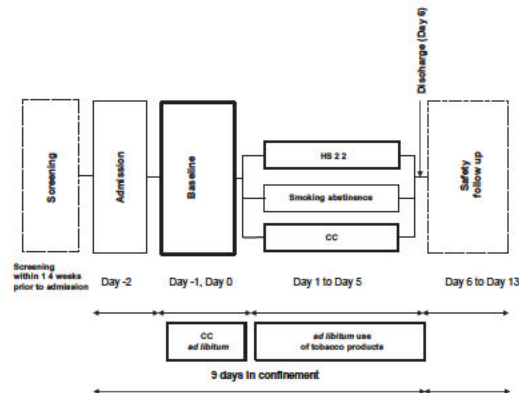
The final decision about subject's qualification is at the investigator's discretion which is based on the available information obtained during the screening.

6. The study design

This is a randomized (assignment to a given group is random), 3-arm, *ad libitum* smoking study to compare the use of THS 2 2 product or smoking abstinence and smoking conventional cigarettes. In total, 160 female and male smoking, but otherwise healthy, subjects will be included into the main study.

Please note: *Ad libitum* use means that you can keep the smoking habits from before the study period i.e. there are no smoking restrictions between 06:30 and 23:00 on the number of conventional cigarettes if you are assigned to conventional cigarette arm or THS 2 2 product if you are assigned to THS 2 2 arm.

The entire study duration will be 17 to 43 days including a screening period of up to 28 days (4 weeks) prior to admission to the clinic (Day -30 to Day -3), a 9 day stay at the site period (afternoon of Day -2 to morning of Day 6) and a follow-up period (until Day 13) 7 days after discharge on Day 6.

Subject Screening No.: Screening period (Day -30 to Day -3)

The Screening period covers up to 4 weeks (Day -30 to Day -3) prior to Admission to the Site (afternoon of Day -2). A demonstration of the THS 2.2 product will be given by the site staff during the Screening Visit.

Confinement period (Day -2 to Day 6)

You will be in a confined site for 9 days from Day -2 onwards as follows:

- The initial period of admission to the site is defined as from Day -2 (Admission) until 06:29 of Day -1.

After admission to the site at Day -2, as the last procedure of the day to perform final assessment of your eligibility to participate in the study, you will have a trial of the THS 2.2 product (Using up to 3 THS Tobacco Sticks). For female subjects, the trial of the product will be done after pregnancy was excluded. You can only participate in the study if you are willing to take part, and able to use the product.

The 2-day baseline period starts at 06:30 on Day -1 until 06:29 on Day 1. Random assignment (randomisation) to each study arm will be performed by a computer program. You will be informed of the study arm to which you have been randomly selected prior to 06:30 on Day 1 of the study:

- THS 2.2 product (*ad libitum* use) (THS): subjects who will use the THS 2.2 product.
- Conventional Cigarette's (CC): subject who will smoke their own brand cigarettes (*ad libitum* use).
- Smoking Abstinence (SA): subjects who will abstain from smoking. If you are assigned to the SA arm, you will be asked to abstain from smoking any nicotine/tobacco-containing product and you will not be provided with medication to support smoking abstinence. You will be provided with psychological support during the period of smoking abstinence.
- The 5 days exposure period is defined as from 06:30 of Day 1 until 23:00 of Day 5.

Subject Screening No.: End of study procedures and discharge from the site in the morning of Day 6

You will be discharged after 9 days confinement on Day 6, once you have completed all the end of study procedures. Smoking is not allowed from Day 5, 23:01 until spirometry has been performed on Day 6.

Follow-up period (until Day 13)

After the discharge, you will enter a 7-day safety follow-up period during which you will be asked to inform the site about any potential medical events you may experience.

Human Smoking Topography (HST)

As part of the main study described above, you will participate in a Human Smoking Topography procedure (for assessment of human smoking behaviours). Human smoking topography involves the measurement of each smoker's unique way of using THS 2.2 product or smoking CCs by employing the SODIM® portable device. The SODIM® device, model SPA/M (SODIM® Instrumentation, Fleury les Aubrais, France) consists of a special holder which is placed between the smoker's mouth and the filter of the CC being smoked or THS 2.2 product being used and portable data logger. The holder is connected by 2 narrow tubes to a portable data logger/recording system which records among others such parameters as puff volume, number of puffs and puff duration. Smoking Topography will not be done in subjects smoking CC that are incompatible with the HST SODIM® device (e.g. slim cigarettes).

At Day 0, the HST SODIM® device has to be used for all CC smoked for all subjects. On Day 1 and Day 4 of the confinement period, the HST SODIM® device has to be used for every product use for all participants in the CC and THS 2.2 arms.

For each subject, one HST SODIM® device will be assigned at Day -1, which will be used by that subject on all HST assessment days starting from Day 0 (in the case of malfunction, the device will be exchanged).

From Day 1 onwards, for participants in the SA arm, no HST assessments will be performed.

7. Smoking Restrictions and Filters/Butts collection

Only smokers of non-mentholated, commercially available and manufactured conventional cigarettes with a maximum of 1 mg nicotine per cigarette ISO yield are allowed into the study. This is an *ad libitum* product use study; however, the smoking can be restricted if, in the judgement of Investigator, further smoking can be dangerous to you. During the confinement period, with the total of 9 days (from Day -2 to Day 6), smoking is allowed during the designated smoking times, from 06:30 to 23:00, except during study procedures.

You will not have free access to your conventional cigarettes or THS 2.2 product; these will be dispensed by the study site staff individually.

During the baseline period, you will be allowed to continue smoking *ad libitum* your usual conventional cigarettes. During the exposure period, you will be assigned to either continue smoking conventional cigarettes (cigarettes that you smoked before the study and at baseline) or to use exclusively the THS 2.2 product (which is explained within this information sheet) or abstain from smoking.

To avoid cross contamination (that is inhaling cigarette smoke by persons using other cigarettes) between the two smoking arms, users of the THS 2.2 product and of conventional cigarettes must use separate smoking rooms. If you are assigned to the THS 2.2 arm, you will not be allowed to smoke any conventional cigarettes or use any other nicotine/tobacco containing products from 06:30 of Day 1 until 23:00 of Day 5. If smoking of conventional cigarettes or use of any other nicotine/tobacco containing products is detected in this study arm, you will be withdrawn from the study.

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In general, the performance of scheduled procedures has priority over the wish of a subject to smoke during the study. However, this is different at Day 5 due to the assessment of the nicotine profile. If you want to smoke around the time of the blood draw, you should smoke first and the blood will be drawn after the cigarette has been smoked.

Smoking will not be allowed from 23:00 on Day 5, until spirometry has been performed on the morning of Day 6. All examinations of the end of study will be conducted on Day 6 prior to discharge. If you are assigned to the SA arm, you will not be allowed to use any nicotine/tobacco-containing product and you will not be provided with medication to support smoking abstinence.

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

From Day 1 to Day 5, conventional cigarettes butts will be collected for accountability only.

The filters and tobacco plugs of all used THS Tobacco Sticks will be collected from Day 1 to Day 5, using dedicated vials for accountability and subsequent analysis of nicotine retention.

8. Stay at the Site, Allocated Product Use

From the time of admission to the site, you must restrict yourself to smoking only your preferred brand of conventional cigarettes. During the period of admission to the site (Admission to site until 06:30 of Day-1) and the baseline period (06:30 at Day-1 until 06:29 of Day 1), you will continue smoking your own preferred single brand of commercially available non-mentholated conventional cigarettes with a maximum yield of 1 mg nicotine ISO/CC.

Conventional cigarettes will not be provided by the Sponsor or site staff. You will be asked to purchase your own preferred single brand conventional cigarettes for the confinement period prior to Admission. As random assignment for the main study takes place on the evening of Day 0, you need to provide your anticipated amount of conventional cigarettes for a total of 9 days plus two extra packs at Day -2 (Admission day) to the site staff.

The cigarette packs provided by you should not be opened and the cellophane wrapper should be intact. Each pack of cigarettes provided by you will be labelled to identify which subject the cigarettes belong to. The unused conventional cigarettes will be given back to you at discharge.

THS 2.2 product will be provided by the Sponsor.

Every person who is willing to make a quit attempt during the study will be encouraged and adequate support will be given.

9. Dietary Restrictions and Meals

A standard diet will be designed by a dietician for the whole confinement period. In order to avoid any effect on assessment of biomarkers of exposure, grilled or pan-fried meat, pre-cooked meats (e.g. tuna, ham, corned beef, and smoked meats), bacon and sausage will not be permitted. In addition, alcohol, broccoli, brussels sprouts, cauliflower, grapefruit and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana, etc.) will not be allowed except when you are asked to drink a cup of coffee for one of the assessments (you will be instructed accordingly by your site staff). Consumption of quinine-containing drinks (e.g. tonic water) is not allowed during the study.

You are not allowed to bring your own food (including sweets or chewing gum, etc.) or beverages to the site. Meals will be served according to the agreed schedules. Consumption of non-carbonated water is allowed as desired.

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Fasting state has to be observed for at least 8 hours prior to blood draws for the safety laboratory and the long term storage of serum/plasma at the Screening Visit, on Day 0, and on Day 6

Meals will be served according to the study plan

Planned menus for the whole confinement period will be presented upon admission to Site

10. Concomitant Treatment

No medication must be taken during the study without prior information 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.

11. Questionnaires and Visual Analogue Scales (VAS)

Throughout the study you will be asked to complete a variety of questionnaires and visual analog scales (VAS). The VAS requires that you make a mark on a line to indicate an answer to a question. The questionnaires and the VAS will be answered by you directly in an electronic (ePRO device) or in paper diary.

The study site staff will provide you with detailed instructions of how to use the ePRO device and how to complete the paper diaries in which you will record your responses to the questionnaires and VAS. The questionnaires and the VAS will be reviewed for completeness by the site staff and you will be requested to complete any missing information.

12. Study Schedule

Screening visit (duration about 3-4 hours for one Subject)

- Subject identification (ID required)
- Information on the risk of smoking and advice on smoking cessation
- Informed consent
- Demographic data collected (gender, date of birth/age, and race)
- Willingness to quit smoking within the next 3 months (you will be asked a question if you are planning to quit smoking during the next 3 months) and readiness to abstain from smoking for at least 5 days
- Identification of current conventional cigarette brand (the site staff will document brand name (s) and nicotine, tar and CO yields)
- Medical history/concomitant disease (any condition that started prior to and ended prior to Screening Visit)
- Prior medication taken on the visit day, including hormonal contraceptives, (taken by you within 4 weeks of Screening Visit)
- Smoking history
- Vital signs (blood pressure, heart rate, respiratory rate)
- Collection of blood and urine samples in order to perform laboratory tests (haematology, biochemistry – after at least 8 hours fasting period, a general urine test, serological tests for HIV, hepatitis B and C, test for the presence of addictive and narcotic substances, as well as nicotine metabolite in urine, urine pregnancy tests for women)
- You will be asked to notify of any adverse health or medical events, referred to as adverse events;
- Physical examination, including height, weight, calculation of BMI
- For female subjects urine pregnancy test and verification of contraceptive method used

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- THS 2 2 product demonstration (the product will be demonstrated by the site staff)
- Chest X-ray (if not performed 6 months prior to Screening Visit): you will be referred for this procedure to a radiology unit
- Alcohol breath test (using an alcometer device)
- A questionnaire for nicotine dependence
- Spirometry (measuring of your lung function) with and without short-acting bronchodilator (an inhaled medication that relaxes the muscles in the lungs and widens airways), the test will be performed after at least 1 hour since the last cigarette;
- Electrocardiogram – a painless tracing of your heart rate & rhythm (ECG)

Admission Day -2

- Collection of urine samples in order to perform laboratory tests (test for the presence of addictive and narcotic substances, as well as nicotine metabolite in urine, urine pregnancy tests for women)
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events
- Information on the risk of smoking and smoking cessation advice
- Smoking history
- You will be asked to notify of any adverse health or medical events, referred to as adverse events
- Alcohol breath test (using an alcometer device)
- Willingness to abstain from smoking for at least 5 days
- CO breath test (measurement of the amount of carbon monoxide in the breath)
- Vital signs (blood pressure, pulse rate, respiratory rate)
- Physical examination (including weight, BMI)
- Trial of THS 2 2 product (as the last procedure of the eligibility criteria you will have a trial of THS 2 2 (using up to 3 Tobacco Sticks)
- Identification of current conventional cigarette brand (you will have to hand your conventional cigarettes supply for the confinement period to the site staff, who will take a photograph of the front and of the side (bearing the tar, nicotine and carbon monoxide yields) for documentation)

Baseline Day -1

- Start of the 24-hour urine collection (each time you will urinate in to 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
- CO breath test (four times per day; first test to be performed 15 minutes prior to the first smoking event, the other tests to be done around 12 00, 16 00 and 20 00), a sample for carboxyhemoglobin (COHb) (measurement of carbon monoxide concentration in the blood – around 20 00)
- Vital signs (blood pressure, heart rate, respiratory rate)
- You will be asked to notify of any adverse health or medical events, referred to as adverse events
- Questionnaire of Smoking Urges - You will be asked to complete a questionnaire to indicate your smoking urges
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire to evaluate your smoking experience/using THS 2 2 product Baseline Day 0

In addition to the Day D-1 procedures the following will also be performed at Day D 0:

- Collection of blood samples for Day 0 as follows:

Subject Screening No.:

- Sample for haematology and biochemistry (safety samples - to ensure that you are fit and healthy to be enrolled in the study) - to be taken after at least 8 hours of fasting (approx 06:30am)
- Sample for long-term storage (after at least 8 hours of fasting if you gave consent for this sample – approx 06:30 am)
- Sample for transcriptomics analysis (if you gave consent for this sample – approx 15 minutes before your first cigarette)
- Sample to measure the CYP2A6 activity in your blood (approx 06:30 am)
- Sample to measure the CYP1A2 activity in your blood (approx 16:00 pm)
- Sample to measure carboxyhemoglobin (COHb) (a measure of carbon monoxide levels in your blood) – (approx 20:00pm)
- Sample to measure the nicotine/cotinine levels in your blood (approx 20:00 pm)
- Spirometry (measuring of your lung function) – without bronchodilator Please note that you will not be able to smoke your first cigarette of the day until your spirometry assessment is performed. As a result of this your first cigarette may not be smoked until 11am
- You will be asked to notify of any adverse health or medical events, referred to as adverse events. A sample of your urine will be taken (between 6:30 and 12:30) for safety to ensure that you are fit and healthy to be enrolled in the study
- HST questionnaire – you will be asked to complete a questionnaire to evaluate the use of HST on your smoking rituals. Applicable if you smoke conventional cigarettes that are compatible with the HST device
- Assessment of Cough - you will be asked to complete a questionnaire assessing your cough
- Minnesota Nicotine Withdrawal Scale – (MNWS) you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal
- Nicotine Craving Questionnaire – the participants will complete a questionnaire about nicotine cravings
- Modified cigarette evaluation questionnaire – the participants will complete a questionnaire to evaluate their experience related to smoking/THS 2.2 product use
- Drink a cup of coffee containing approximately 150mg of caffeine

Please note the HST SODIM® device has to be used for all smoking events on Day 0 if compatible conventional cigarettes are smoked. All smoked conventional cigarettes butts will need to be collected for accountability

Exposure period Day 1 to Day 5

- Random assignment to THS 2.2, CC or SA arm You will be notified of which study arm you have been randomly allocated to prior to 06:30 on the morning of Day 1
- Start of the 24-hour urine collection is on Day 1 until the morning of D6 (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 (Day 1 to Day 6)
- Blood samples will be collected to measure values of Biomarkers in the blood. The Biomarkers to be researched are known as COHb and Nicotine and Cotinine.
Collection of blood samples as follows:
COHb – Day 1 to Day 4, one blood sample in the evening around 20:00 Day 5, one blood sample within 15 minutes prior to smoking/using your first cigarette of the day and at approximately 08:00 in the morning for participants in the smoking abstinence arm, followed by a further three blood

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samples at approximately 12 00, 16 00 and 20 00 for all participants

Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening at approximately 20:00 each day Day 5, THS 2.2 and CC arms only, one blood sample within 15 minutes prior to smoking/using your first cigarette of the day followed by a further eight samples at 2 hour intervals On Day 5 subjects assigned to smoking abstinence, one blood sample in the morning at approximately 08:00

- CO breath test (four times per day; first test to be performed 15 minutes prior to the first cigarette smoking/using event and between 8:00 and 10:00 for participants in the smoking abstinence arm, the other tests to be done around 12 00, 16 00 and 20 00) (Day 1 to Day 5) for all participants
- Vital signs (blood pressure, pulse rate, respiratory rate) (Day 1 to Day 5)
- You will be asked to notify of any adverse health or medical events, referred to as adverse events
- You will be asked to complete a questionnaire assessing your cough (Day 1 to Day 5)
- You will be asked to complete the HST questionnaire (if you are assigned to the THS 2.2 or CC arm) (Day 4 only)
- Minnesota Nicotine Dependence/Withdrawal Scale (MNWS) – the participants will complete a questionnaire to evaluate symptoms of nicotine withdrawal (from Day 1 to Day 5)
- Nicotine Craving Questionnaire – the participants will complete a questionnaire about nicotine cravings (Day 1 to Day 5)

Modified cigarette evaluation questionnaire – the participants will complete a questionnaire to evaluate their experience related to smoking/THS 2.2 product use (THS 2.2 and CC arm participants from Day 1 to Day 5)

Please note the HST SODIM® device has to be used for all smoking events/THS 2.2 product use by participants assigned to THS 2.2 and CC arms if compatible conventional cigarettes are smoked (Day 1 and Day 4) and for compatible CCs smoked at Day 0

Please note that all used THS 2.2 products and conventional cigarettes butts will need to be collected (Day 1 to Day 5) In the THS 2.2 arm, subjects will be asked to collect every used filter and tobacco plugs into dedicated vials which will be provided by the staff

Discharge from the site - Day 6

- Collection of blood samples (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 participants in the arm abstaining from smoking one blood sample will be taken between 8:00 and 10 00
- End of 24-hour urine collection started on Day 5
- A sample to measure CYP2A6 activity in the blood
- Collection of blood and urine samples in order to perform laboratory tests (hematology, biochemistry – after at least 10 hours fasting period, a general urine test, urine pregnancy tests for women)
- Collection of blood and urine samples for long term storage, provided that the subject gave consent
- Collection of blood sample for transcriptomics analysis, provided that subject gave consent
- Physical examination (including weight, BMI)
- Assessment of Cough - you will be asked to complete a questionnaire assessing your cough
- Minnesota Nicotine Dependence / Withdrawal Scale – the participants will complete a questionnaire to evaluate symptoms of nicotine withdrawal
- Spirometry (measuring of your lung function) without bronchodilator Please note that you will not be able to smoke your first cigarette of the day until your spirometry assessment is performed As

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a result of this your first cigarette may not be smoked until 11am

- CO breath test
- Vital signs (blood pressure, pulse rate, respiratory rate)
- Electrocardiogram – a painless tracing of your heart rate & rhythm (ECG)
- You will be asked to notify of any unfavorable health or medical events, referred to as adverse events
- You will be asked to complete a questionnaire assessing your cough and craving symptoms
- Advice on the risk of smoking and advice on smoking cessation
- Discharge from the site

Follow-up period (until Day 13)

After you have completed all procedures required prior to discharge from the clinic at Day 6, you will enter a 7-day safety follow-up period. Subjects who terminated the study earlier than Day 6 will enter into the follow-up period on the day of their termination. 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 before the discharge from the site.

13. Smoking Cessation Advice

You will be given information on the risks of smoking and advice on the smoking cessation three times during the study: at the screening visit, at admission (Day -2), and at discharge (Day 6).

14. Blood collection

The maximal total volume of blood taken from you during the study will be around 170 ml, which includes all samples necessary for biomarker analysis and 20 ml for safety and repeated analysis, 20 ml of blood for long-term storage of the samples for future analysis of biomarkers and 10 ml for long-term storage of samples for transcriptomics analysis (only if additional consents are given).

This is less blood than that removed during a standard blood donation (approximately 500 ml). It is possible that you may feel some discomfort when the blood samples are being taken.

The blood samples collected will be analysed using a validated method by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples during this period and their subsequent destruction after signature of the Clinical Study Report. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

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.

15. Urine collection

In the study, the single urine samples will be taken for, safety urine analysis, and the presence of addictive and narcotic substances, nicotine metabolites and pregnancy tests for women.

In this study, 24 hour urine collection will also be performed. You will empty your bladders shortly before 06:30 on the study days as described above in the study schedule section. The collection period starts at 06:30 and ends the following day at 06:29. You will be given detailed instructions by the

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investigational site staff

24 h urine collection samples will be used to measure some biomarkers such as MHBMA, 3-HPMA, S-PMA. Monitoring these Biomarkers will show changes in your body that relate to the exposure of an organism to a chemical

16. Urine and Blood Collection for the long term storage

A separate consent (form attached to this information sheet) is provided to you for collection and long-term storage of urine and blood samples for the purpose of additional future analysis of biomarkers. If you disagree for long-term storage of the urine and blood samples, you will still be able to take part in the clinical study if you agree and sign the informed consent form for the study participation.

17. Analysis of Blood and Urine Samples

All blood samples are to be tested at one of two central laboratories (Celerion Global Bioanalytical Laboratory, USA and Celerion Laboratory, Switzerland) with the exception of blood samples to measure how much carbon monoxide is bound to your haemoglobin and the safety laboratory samples which will be tested at a local laboratory in Poland (Laboratorium Medyczne SYNEVO Warsaw, Poland).

The urine dipstick for the safety laboratory will be tested at a local laboratory in Poland (Laboratorium Medyczne SYNEVO Warsaw, Poland).

The tests for urine drug screen, urine cotinine and urine pregnancy for women will be done by the Site. Blood and urine samples for safety laboratory testing that will be kept for approximately 2 months after the analysis, after which they will be destroyed.

All data collected on to the source documentation (the paper records collected for the duration of the study) will be stored by the investigation site in a secure data storage facility. All collected data will be stored by the Site and/or the Sponsor for as long as necessary to allow inspections of the study by registration authorities. All data received by the Sponsor will be anonymous and your personal identifiers will not be shared.

18. Potential benefits

- Participation in the study is not connected with any direct health benefits.
- One indirect benefit is the detailed assessment of your health by a physician. You will receive copies of the results of your tests if you so wish. You will be referred to a proper specialist if the Investigator will take such decision.
- For the time dedicated to commuting to the Site and your stay at the Site during the study you will receive financial compensation as defined below.

19. financial compensation

For most studies we need to recruit extra subjects (reserves) in case another subject drops out at the last minute because of illness, problems with tests or other issues. We cannot guarantee that you will participate in this study and therefore receive full financial compensation.

If we are unable to include you in this study you will receive a compensation which will reflect the time spent in the Site.

- If you participate fully in this study you will receive compensation for your time to the sum of 4500 PLN.
- Participants who discontinue study for reasons other than failure to meet the requirements of the study will be entitled to compensation in the gross amount of 4500 (four thousand five hundred).

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PLN;

- Participants who withdraw from the study for reasons other than failure to meet requirements of the study will be eligible to compensation in the following amount:
 - 300 (three hundred) PLN gross for each completed day starting on day -2 to day 0
 - 600 (six hundred) PLN gross for each completed day from day 1 to day 6
 - in the event of termination of the study by the Sponsor, the participants will receive full compensation of 4,500 (four thousand five hundred) PLN gross;
- If the investigator determines that the participant must refrain from testing for medical reasons, the participant will receive full compensation of 4,500 (four thousand five hundred) PLN gross;
- If your (i) participation in the study is terminated because of failure to meet the requirements of the study, you will receive compensation in the gross amount of PLN 300, regardless of the time spent in the study

Financial compensation will be paid after the completion of all study procedures (within 7 days after the telephone contact concluding the follow-up period)

20. Risks

Smoking cigarettes has harmful effects on health and causes a physical and mental dependence on cigarettes. Smoking contributes to the development of cancer, atherosclerosis, and the occurrence of heart attacks and other diseases of the heart, blood vessels and lungs. It has been proved that smoking shortens life-span; annually about 80 thousand deaths in Poland are directly related to the negative consequences of smoking. Smoking during pregnancy hampers the growth of the child, who is usually smaller at birth and more susceptible to diseases. Moreover, smoking increases the risks of complications during pregnancy, the delivery of a dead child and the sudden infant death syndrome (the so called, crib death syndrome).

An extemporaneous overdose of nicotine may cause: stomach and intestinal disturbances (nausea, vomiting, diarrhoea, and stomach ache), excessive sweating, dizziness and headache, and/or difficulties in breathing.

Smoking tobacco can be 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, too.

During the study some side-effects connected with different procedures performed on you may occur, listed below are some examples:

- Blood sampling - excessive bleeding, fainting, hematoma, paresthesia, or infection
- 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. Any symptoms you may experience whilst using this drug should be reported to the study doctor immediately. Procedures will be carried out according to internationally and scientifically accepted standards.

All these occurrences will be recorded and the Investigators and nurses will introduce certain measures to limit them. During the whole course of the study, a team of trained Investigators and nurses will monitor your health and safety in the study.

If, for any reason, you consult any physician other than the Investigator during the period from screening visit till the admission to the Site or within 7 days after your discharge from the Site, please inform the Investigator from the BioVirtus Site about any health problem you experience. At any time

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you can inform any physician other than the Investigator about your participation in this study

There is a possibility that the tests performed during the study will find a medical condition or abnormality which you did not know about. If this happens the Investigator will discuss the results with you, arrange appropriate treatment and/or, with your permission, refer you to the specialist medical doctor.

Please note that all doctors (Investigators) employed by the investigation site are trained and experienced in Advanced Life Support Procedures (resuscitation) in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures.

21. General information

a Insurance

The civil liability of the Sponsor has been insured with a third party insurance (policy No (b) (4) issued by Axa Corporate Solution, Polish branch: AXA Towarzystwo Ubezpieczeń, ul. Chłodna 51, 00-867, Warsaw, Poland. Tel: 0048225550075.) The insurance covers the civil liability of the Sponsor for causing bodily harm, disorder or death of the study Subject through the conduct of the study only during the Sponsor's period of insurance coverage.

The Site has retained civil liability insurance for the Investigator and the entire research team (policy (b) (4) issued by Towarzystwo Ubezpieczeń i Reasekuracji Allianz Polska S.A., ul. Rodziny Hiszpańskich 1, 02-685 Warszawa, Tel. 801 10 20 30). The insurance covers the civil liability of the Investigator for causing bodily harm, injury or death of the study participant through the conduct of the study only during the term of the insurance policy retained by the Site.

If, as a result of the negligent action or omission of the Sponsor or the Investigator you experience any damage then you are entitled to seek compensation. You may report it to the insurers of the Sponsor or Investigator or through the Site to the Sponsor. The amount of compensation will be settled according to Polish civil law.

b Withdrawal from the study

Participation in this study is entirely voluntary and you have the right to withdraw from further participation at any time without providing a reason. You may request that all previously retained samples be destroyed to prevent further analysis. Your refusal to participate or withdrawal from the study will not result in any loss of rights to which you are otherwise entitled. If you decide to withdraw from the study, we kindly ask you to inform the Investigator about this fact immediately. In this case, you will be asked to undergo a final medical examination including laboratory tests and perform the assessments planned for the Day of Discharge (Day 6).

c Termination of participation

Possible reasons:

- Withdrawal of informed consent
- Any side effects or condition (including clinically significant changes in a laboratory which in the discretion of the Investigator does no longer justify the participation in this study)
- Positive pregnancy testing (no invasive procedures including the drawing of blood must be performed after detection of pregnancy)
- Withdrawal is considered by the Investigator to be in the best interest of the subject or the other subjects
- The Sponsor or Investigator terminates the study
- You may be discontinued from the study for any of the following reasons:

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- When the research team loses contact with the participant
- When it is necessary to use treatment tahr is not allowed in the study (in general, any concomitant treatment should be discussed with the Investigator on an ongoing basis)
- Detection of smoking conventional cigarettes or use of tobacco-containing products other than the products the participant is assigned to and that is distributed by the Site personnel
- Non-compliance with the study procedures
- Taking the photos and/or recording is prohibited during your stay at the Site and will be the subject for exclusion from the study

d Termination of the study

- The study may be terminated by the Sponsor at any time
- The study may be terminated by the Investigator or the Sponsor, in case of obtaining new data about the safety of the used product, or if the number or intensity of adverse events (any unfavourable and unintended medical event occurring in participants), in the Investigator's opinion, may influence the safety of the participants

If the study is terminated, you will be informed about it, and appropriate measures to protect your health will be undertaken

e Obtaining additional information

If you have any questions related to this study, your scope of rights and duties, as well as how to report potential damages resulting from your participation in the study, please, present them to the Principal Investigator – Dr Katarzyna Jarus-Dziedzic, at BioVirtus Research Site Sp z o o, phone +48 22 101 07 54 from 9 a.m. till 5 p.m., fax +48 22 101 07 56. In emergency situations, you may call the Investigator at any time at the phone number: +48 606 959 140

In case of the occurrence of new additional information related to study product which may influence your decision or willingness to continue participating in the study, the Investigator commits himself/herself to transfer such information to the Participant immediately

Persons, who have been enrolled in a clinical study or have already been Subjects have entitlements which result from the patient rights included in the Card of Patient Rights. Information about this subject is available at the Office of Patients' Rights, appointed by the Minister of Health at 0-800 190 590. The info line is a toll-free telephone line, open from Monday through Friday from 9 a.m. to 9 p.m. Call info line 0 801 108 108 to receive help in quitting smoking

f Duties of the Participant

It is the duty of the Subject 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, to treat the personnel of the Site and other participants of the study with respect, provide reliable information related to the participation in the study, as well as to report to the Site on time. During the stay at the Site, the Subjects are not allowed to invite guests and must not leave the Site premises, with the exception of rooms dedicated for smoking or for the organized strolls under medical supervision. Taking pictures and making recordings at the Site is strictly prohibited or else one will be immediately excluded from the study. Participants staying at the Site must observe the Site Regulations that will be provided to you.

22. Confidentiality of personal data

Your personal data will be treated as confidential, which means that the Investigators and the personnel of the Site are obliged to protect this data and not to disclose it to unauthorized people. With regard to

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your safety, access to the data will be granted to persons monitoring this study, the Sponsor's representatives, Bioethics Committee's representatives, employees of the clinical laboratory and radiological facility as well as other persons authorized by official authorities (e.g. courts, prosecution service). Maintaining confidentiality of data also relates to publications of the study results. Blood and urine samples collected for the identification of biological indicators of exposure to cigarette smoke will be labelled in such a way as to ensure complete anonymity of the person from whom the samples were collected. Your doctor will be informed about a person's participation in the clinical study if the Participant expresses such a wish. Consent for processing your personal and medical data and information about the Data Administrator are included in the form below.

Subject Screening No.: **Personal and Medical Data Protection Form**

I hereby acknowledge and confirm that I have received the following information:

I. Personal data protection

Pursuant to Personal Data Protection Law, Art 24 Item 1, of August 29, 1997 (Journal of Laws No 133 Item 883 as amended), Law dated 22 January 2004 about changes of Data protection Law (Dz. U. 2004 Nr 33 poz. 285) and 95/46/EC European Directive:

- 1 The Data Administrator shall be BioVirtus Research Site Sp. z o.o., Mokra 7, 05-830 Kajetany, Poland
- 2 The personal data will be collected in order to pay financial compensation for my participation in the medical experiment (Protocol No. ZRHR-REXC-03-EU)
- 3 I am entitled to inspect and correct my data as provided by the Personal Data Protection Law of August 29, 1997 (Dz.U.Nr.133 poz.883 and further amendments)
- 4 Personal data will be kept for at least 15 years after the end of the study or longer if required by local regulations

II. Medical data protection

1 My medical data obtained in the course of the medical experiment (Protocol No. ZRHR-REXC-03-EU) which was obtained for scientific-cognitive purposes, may be made available only to those persons listed below who are obliged to keep professional secrecy, and who are obliged to treat this data as confidential:

- authorized employees of BioVirtus Research Site Sp. z o.o. (Investigators, nurses, coordinators) and subcontractors (authorized employees of the clinical laboratory and radiological facility)
- authorized representatives of the study Sponsor (Philip Morris Products S.A.)
- persons monitoring the study
- and people conducting inspections of the study
- members of the Bioethics Committee, other people authorized by official authorities

And in respect of which, I hereby grant my consent

- 2 The results of the medical experiment in which I will participate will be presented in such a form that anonymity of Participants will be ensured
- 3 I consent to my data being used for scientific purposes, as described in this Subject Information
- 4 My medical data, labelled in a way so as to ensure anonymity, will be sent to the authorized representatives of the study's Sponsor (Philip Morris Products S.A.) and maintained in a secure database

I submit my data of my own free will

To be filled out by the Participant:

Signature dd mm yyyy hour: min



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Subject Screening No.: **INFORMED CONSENT FORM
CONSENT FOR COLLECTION AND LONG-TERM STORAGE OF BLOOD
AND URINE SAMPLES**

Title: A randomized, controlled, open label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing use of conventional cigarettes, for 5 days in confinement

First name and family name of the Subject (to be filled out by the Subject, legibly, in print)

I have been informed that:

- No genetic testing will be performed on the stored biological material
- All samples will be stored until the Sponsor issues consent for their destruction, which will be performed by a company contracted by the Sponsor or the Site

☐ I give my consent for the collection of 20 ml of blood and storing in a designated laboratory for 5 years and for collection and storing of 100 ml of urine for 2 years counting from the signing of the final study report, in order to perform additional analyses

To be filled out by the Subject:

Signature dd mm yyyy hour: min

To be filled out by the Investigator:

Signature dd mm yyyy hour: min

☐ I do not give my consent to the collection, and storing, in a designated laboratory of 20 ml of blood for 5 years and 100 ml of urine for 2 years counting from the signing of the final study report, in order to perform additional analyses

To be filled out by the Subject:

Signature dd mm yyyy hour: min

To be filled out by the Investigator:

Signature dd mm yyyy hour: min



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SUBJECT INFORMATION AND INFORMED CONSENT FORM**OPTIONAL TRANSCRIPTOMIC RESEARCH STUDY****Study: ZRHR-REXC-03-EU**

Principal Investigator: Katarzyna Jarus-Dziedzic MD, PhD

Site: BioVirtus Research Site Sp. z o.o.

Address: Mokra 7, 05-830 Kajetany, Poland

Tel: +48 22 101 07 54

Fax: +48 22 101 07 56

Study Title: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement.

1. Introduction

You have already agreed to participate in the main study, involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of a new modified risk tobacco product (MRTP) THS 2.2 on selected biomarkers of exposure (BoExp) compared to conventional cigarettes.

This form tells you about an optional assessment which will be conducted in subjects that are already participating in the main study. This patient information and informed consent form is an addition to the main study form that you have already signed. The intention of this document is to ask you consent for collection, storage of blood samples for long-term storage and for your consent to use these samples for transcriptomic testing.

The optional transcriptomic testing is explained below:

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. One of the roles of the family of biological molecules ribonucleic acid (RNA) is to help make these proteins. The optional tests (transcriptomic analysis) described here will involve the determination of the number and quality of that RNA, in all its forms, in blood samples from healthy subjects to understand if the harmful effect of smoking conventional cigarettes on the function of cells could be decreased when switching to the THS 2.2 test product. This transcriptomic testing will help understand how people respond to different exposure types (i.e. conventional cigarettes compared to test product).

Transcriptomic testing is different from genetic testing done for the purpose of diagnosing a person with a certain disease, or for risk for developing a certain disease.

Your study doctor, or study staff, will go over this with you and answer any questions you may have regarding this optional part of the 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. No one can force you to agree on this optional transcriptomic testing. If you do not agree to participate, you can still continue to participate in the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the optional study. This form is not meant to replace the one for the main study, and the contents of the main study subject information applies to this optional transcriptomic testing.

By signing this informed consent form you agree for collection, storage of blood samples for long term and that transcriptomic testing may be done on your samples.

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 optional study.

Before you decide to take part, you must understand the purpose of this optional transcriptomic testing, how your participation may help you, any potential risks to you, and what is expected of you during this sub-study. Even if you agree to participate in this optional assessment you are free to change your mind and stop at any time without penalty or loss of benefits which you would otherwise have.



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2. What is the purpose of the optional study test?

If you consent to this optional study test, two blood samples for this type of analysis (transcriptomic testing) will be drawn. 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 6). These samples will be sent to the designated laboratories listed below in Section 4 to investigate how your RNA is affected by using the THS 2.2 product in comparison to smoking conventional cigarettes during your stay at the clinic site.

3. What will happen to me if I take part?

If you wish consent to this optional transcriptomic assessment, the study doctor will ask you to sign a separate informed consent form. By signing this form, you will give consent to this optional part of the study that is to give two blood samples (two 5ml tubes = 10 ml in total) for long-term storage with the purpose of transcriptomic testing. You will not be able to take part in this optional test unless you sign the consent form. In the unlikely case that there is a problem processing your sample, you will not be asked to give an additional sample.

4. Sample Analysis and Storage

Your two blood samples will be shipped for storage and analysis to a laboratory contracted by the Sponsor (Philip Morris Products S.A.) which has experience in such testing as well as retaining and storing samples such as these. The blood samples will be stored in a dedicated repository for clinical samples in Germany and further analyzed in a designated laboratory using appropriate methods.

Laboratory in which the samples will be stored:

• Tel: (b) (4)
Fax: (b) (4)

Laboratory which will undertake the analysis will be required to follow the requirements as set out in this informed consent form.

5. Sample Access Rights

Your blood samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. All blood samples will be coded and the link between you and the code will be removed once all checks of the sample and related study paperwork are complete. It will happen before the samples are sent to the laboratories.

Once the link has been removed it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Removing the link between the samples and individual participants is intended to prevent your re-identification. As anonymous 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 one is done after removal of link between data. Only your study doctor or study team members will be able to trace the samples back to you, and only until the time at which the samples are sent to the laboratories.

6. Post-Study Sample Handling

Samples will be transferred to the Sponsor's laboratories in Germany and laboratory which will perform the analysis. The samples will be used until no further analyses are possible or the maximum storage time has been reached (15 years). 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.

7. What are the possible disadvantages and risks of taking part?

Using a needle to remove blood from a vein is called "a blood draw." It may be necessary to try more than once. A new needle will be used for each blood draw. Blood samples for transcriptomics will be taken twice during the study. You might feel pain or be light-headed from this. You may experience some temporary discomfort, bleeding, bruising, or rarely, infection, at the site of a needle stick you receive in the process of drawing blood samples.



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8. What are the possible benefits of taking part?

There is no direct benefit to you by taking part in this optional 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 transcriptomic tests performed on the sample that you provide for this research.

9. Is taking part in this optional assessment voluntary?

Taking part in this transcriptomic study is voluntary. You may withdraw your consent to take part in it whilst you are involved in the study without affecting your participation in the main study, and without any penalty or loss of benefits to which you are entitled. To withdraw your consent, you must contact your study doctor Katarzyna Janus-Dziedzic on +48 606 959 140, because only she has access to all of your identifying information.

Your study doctor will keep records that link your personal information with your coded blood sample and health information until all the information about the samples has been checked at the end of the study. Then, the link will be removed. If you withdraw your consent for transcriptomic analysis prior to deletion of the list, you may request your blood samples to be destroyed by the researchers and no longer used in the study. After these records linking your identity to your sample have been checked and subsequently destroyed, it will no longer be possible for the researchers to destroy your sample and the related data if you withdraw your consent since the samples will already be anonymous.

The researchers shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

10. What if there is a problem?

If you have a concern about any part of this optional assessment, you should ask to speak with the study doctor and his/her team who will do their best to answer your questions. Pursuant to the laws and regulations in force, the Sponsor's liability insurance have been covered by a third-party insurance (Policy No. (b) (4) issued by Axa Corporate Solutions, Poland Branch: AXA Insurance Company, ul. Chłodna 51, 00-867, Warsaw, Poland, Phone: 0048225550075). The site has liability insurance includes liability of the investigator and entire study team (Policy No. (b) (4) issued by Insurance Company and Reinsurance Allianz Poland S.A., ul. Rodziny Hiszpańskiej 1, 02-685 Warsaw, Tel. 801 10 2030). For detailed information please refer to the General Information section of the main study subject information and informed consent form for the main study under the heading „Insurance”.

11. What other options are there?

You have the choice not to take part in this transcriptomic research.

12. Can I change my mind?

You may withdraw your consent to the use of your blood samples for this optional transcriptomic research whilst you are still undergoing study assessments until the end of the study by contacting your study doctor/nurse. If you withdraw your consent prior to the end of the study, the study doctor will arrange to have them destroyed. If you withdraw your consent after the end of the study, the destruction of your samples and the related data may not be possible.

13. Will my taking part in this optional assessment be kept confidential?

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. Blood samples sent for analysis to the study site will not include your name or any other personal details that could identify 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.

14. What will happen with the results of this optional assessment?

This transcriptomic research is not intended to provide you with clinical information. Although you
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have the right to access information in your medical records, the information that the researchers will maintain in their databases and create during transcriptomic testing is for research purposes only. The researchers will not return any transcriptomic information to you or your study doctor. **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 identified in any such publication as your samples will remain anonymous.

15. Development for Commercial Gain:

Your study doctor/study site will be reimbursed for obtaining the blood sample for this transcriptomic research and transferring your study information to the researchers. Any information resulting directly or indirectly from this transcriptomic research, as well as any rights in law, diagnostic tests, drugs, or biological products developed or created directly or indirectly as a result of this research, are the exclusive property of the Sponsor (and any of its successors) and may be used for commercial purposes anywhere in the world. You have given all and any rights you may have had to this property and these rights or any share of the profits that may be earned directly or indirectly as a result of this transcriptomic research exclusively to the Sponsor. You will receive no personal recognition or payment. However, in signing this form and donating blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

16. Who is organising and funding the research?

The company sponsoring this optional assessment is Philip Morris Products S.A. (including agents, contractors or consultants).

17. Who has reviewed the study?

An independent ethics committee has reviewed the objectives and the proposed conduct of the main study and of this optional transcriptomic research study and has given a favourable opinion of it.

18. Contact details

If you have any questions regarding this sample collection or transcriptomic research you should contact your study doctor Katarzyna Janus-Dziedzic on +48 606 959 140

If you have any questions relating to privacy, ethical issues, potential conflicts of interest of the study doctor, or your rights as a research subject, you should contact the Patient Right Bureau at the Ministry of Health. Please note that subjects who have been enrolled or are already participating in the study have the rights resulting from Patient's Right specified in Patient's Bill of Rights. You may receive further information in this matter on a free of charge phone number: 0-800 190 590 (Monday to Friday from 9 a.m. to 9 p.m.).

Thank you for taking time to read this information sheet.

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INFORMED CONSENT FORM**Study: ZRHR-REXC-03-EU**

Study Title: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement.

First name and family name of the Subject (to be filled out by the Subject, legibly, in print)

.....

Please tick each box to confirm that you have read each statement

I hereby confirm that:

- ☐ I confirm that the optional transcriptomic assessment has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.
- ☐ I confirm that I have read and understand the information sheet Polish final version 1.0 dated May 7, 2013 for the transcriptomic study.
- ☐ I understand that my participation is voluntary and agree to take part in this transcriptomic study.
- ☐ I agree for collection and long-term storage of 10 ml blood.
- ☐ I agree that my blood sample can be used for the purposes of this transcriptomic assessment.
- ☐ I understand that the link between myself and my transcriptomic blood sampling will be destroyed at the end of the study and before sending the blood samples to the researchers for analysis or the storage facilities.
- ☐ I understand that if I withdraw my consent for the transcriptomic assessment, it will not be possible to destroy both my blood samples and the data obtained from my samples from deletion of the link between my personal data and the blood sample.

A copy of this Information Sheet and signed Consent Form will be given to you to keep.

To be filled out by the Subject:

Signature dd mm yyyy hour : min.

To be filled out by the Investigator:

Signature dd mm yyyy hour : min.

16.1.3.19 SUBJECT INFORMATION AND INFORMED CONSENT FORM POLISH

The following versions of the ICF were used in the study:

Final v1.0 03 May 2013 Main Study

ICF Transcriptomics v1.0 07 May 2013

