PMI RESEARCH & DEVELOPMENT

Statistical Analysis Plan

Study Title:	A cross-sectional study to demonstrate favorable differences in Biomarkers of Potential Harm following at least one year of Tobacco Heating System (THS) use compared to cigarette smoking
Study Number:	P1-RMC-03-INT
Product Name:	Tobacco Heating System (THS)
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	1.0
Date:	14th January 2020

STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

When this page is signed the Statistical Analysis Plan (SAP) is considered final. The signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

CRO Approval:

[redacted], Principal Statistician DocuSigned by: [redacted] A0D66D9CDD10478... 1/14/2021 {Signature_Date} [redacted]	[redacted], Senior Statistician II DocuSigned by: [redacted] 1/18/2021 {Signature_Date} [redacted]

Sponsor Approval:

[redacted], Manager Biostatistics DocuSigned by: [redacted] 94B3F83767494BD... {Signature_Date} Philip Morris Products S.A.	[redacted], Study Scientist DocuSigned by: [redacted] 2493F053001B4D5... 2/1/2021 {Signature_Date} Philip Morris Products S.A.
[redacted] Senior Medical Safety Officer DocuSigned by: [redacted] 4D7997E3BA35428... 2/1/2021 {Signature_Date} Philip Morris Products S.A.	[redacted], Senior Biostatistician DocuSigned by: [redacted] 2/1/2021 {Signature_Date} Philip Morris Products S.A.

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1 INTRODUCTION

This statistical analysis plan (SAP) has been developed to supplement the statistical analyses described in the clinical study protocol (final version 2.0) dated <dd Month 2020>.

The SAP contains a complete and detailed specification of the statistical analyses. A detailed description of the planned Tables, Figures and Listings (TFLs) will be provided in a separate TFLs shell document. Any changes to the TFL shell numbering or to the title of the TFLs will not require an amendment to this SAP.

This SAP and any amendments will be finalized prior to the lock of the clinical database. Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be described in the clinical study report (CSR).

1.1 Rationale

The purpose of this study is to demonstrate favorable differences in three biomarkers of potential harm (BoPH) associated with inflammation, oxidative stress, and arterial stiffness, and indicative of health benefit, in Asian and European healthy subjects who have switched from cigarettes to THS for at least one year compared to cigarette smoking. Additional BoPH associated with cardiovascular and respiratory diseases will be assessed to provide a comprehensive insight into overall health benefit, as well as self-reported behavioral outcomes related to tobacco/nicotine-containing products use, in THS users, cigarette smokers, and former cigarette smokers.

1.2 Revision History

Version	Date of Revision	Revision
1.0	14January2021	Initial Final Version

2 ABBREVIATIONS OF TERMS

AE	Adverse event
AIx	Augmentation index
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic and Chemical
BD	Bronchodilator
BMI	Body mass index
BoExp	Biomarker of exposure
BoPH	Biomarker of potential harm
BP	Bodily pain
CC	Current cigarette smokers
CD	Compact disc
CEMA	2-cyanoethyl mercapturic acid
CI	Confidence interval
Cig	Cigarette(s)
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COPD	chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTMS	Clinical trial management system
CV (statistics)	Coefficient of variation
CVD	Cardiovascular disease
DMP	Data management plan
DNA	Deoxyribonucleic acid
11-DTXB2	11-dehydrothromboxane B2
ECG	Electrocardiogram
8-epi-$PGF_{2\alpha}$	8-epi-Prostaglandin-$F_{2\alpha}$
ePRO	electronic patient reported outcome
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration

FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1 second
FMD	Flow-mediated dilation
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
GH	General health
HbA1c	Glycated hemoglobin
HCY	Homocysteine
HDL-C	High-density lipoprotein cholesterol
HPHCs	Harmful and potentially harmful constituents
hsCRP	high-sensitivity C-Reactive Protein
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IP	Investigational product
IRB	Institutional Review Board
LDL-C	Low-density lipoprotein cholesterol
LLOQ	Lower limit of quantification
LS	Least squares
MCS	Mental component score
MDA	Malondialdehyde
MedDRA	Medical dictionary for regulatory activities
MH	Mental health
MPO	Myeloperoxidase
MRTP	Modified risk tobacco product
NEQ	Nicotine Equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NRT	Nicotine replacement therapy
ox-LDL	Oxidized low-density lipoprotein
PCS	Physical component score
PF	Physical functioning
PMI	Philip Morris International

PP	Per-Protocol Analysis Set
PRO	Patient-reported outcome
PT	Preferred term
PWV	Pulse wave velocity
QC	Quality control
RE	Role-emotional
RP	Role-physical
RRP	Reduced risk product
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Smoking cessation
SD	Standard deviation
SES	Socioecenomic status
SF	Social functioning
SHM	Sample handling manual
sICAM-1	Soluble intercellular adhesion molecule-1
SOC	System organ class
SOP	Standard operating procedure
suPAR	soluble urokinase Plasminogen Activator Receptor
TC	Total cholesterol
TG	Triglycerides
THS	Tobacco Heating System
TNF-α	Tumor Necrosis Factor-α
TNP	Tobacco and/or nicotine containing product
UBC	United BioSource Corporation
ULOQ	Upper limit of quantification
V	Visit
VAS	Visual analogue scale
VT	Vitality
WBC	White blood cell (count)
WHO	World Health Organization

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

The primary objective of this study is:

To demonstrate favorable differences in Biomarkers of Potential Harm (BoPH) associated with inflammation, oxidative stress, and arterial stiffness, in THS users compared with cigarette smokers.

Endpoints:

- White Blood Cell total count (WBC) in blood,
- 8-epi-Prostaglandin-$F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) in urine (expressed as concentration adjusted to creatinine),
- Augmentation Index (AIx).

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

1. To determine the differences in BoPH indicative of the multiple mechanistic pathways associated with main smoking-related diseases between THS users and former cigarette smokers compared to current cigarette smokers.

   Endpoints:

   - Inflammation: WBC (between cigarette smokers and former cigarette smokers only), high-sensitivity C-Reactive Protein (hs-CRP), Homocysteine (HCY),
   - Oxidative stress: 8-epi-$PGF_{2\alpha}$ (between cigarette smokers and former cigarette smokers only), Myeloperoxidase (MPO),
   - Lipid metabolism: High-Density Lipoprotein Cholesterol (HDL-C), Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), oxidized Low-Density Lipoprotein (ox-LDL),
   - Endothelial dysfunction: soluble Intercellular Adhesion Molecule-1 (sICAM-1), Flow-Mediated Dilation (FMD) (only in selected centers),
   - Platelet activation/Coagulation: Fibrinogen, 11-dehydrothromboxane B2 (11-DTXB2),
   - Arterial stiffness: AIx (between cigarette smokers and former cigarette smokers only) and Pulse Wave Velocity (PWV),

- Lung function (spirometry with and without bronchodilator): forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$)[absolute and % predicted values, where applicable],
- Cough assessment questionnaire.

2. To determine the levels of BoExp to harmful and potentially harmful constituents (HPHCs) and nicotine in THS users, cigarette smokers and former cigarette smokers.

   Endpoints:

   - BoExp to HPHCs and nicotine: Carboxyhemoglobin (COHb) in blood, total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL), Nicotine Equivalents (NEQ), and 2-Cyanoethyl Mercapturic Acid (CEMA) in urine (all three expressed as concentrations adjusted to creatinine).

3. To describe the self-reported perceptions and behaviors related to tobacco product use in THS users, cigarette smokers and former cigarette smokers.

   Endpoints:

   - Scores of the different self-reported instruments from the ABOUT Toolbox assessing:
     - Perceived Risk (Health Risk),
     - Perceived Dependence (Extent of Use, Signs and Symptoms, Behavioral Impact) (between THS users and cigarette smokers only).

4. To describe the generic self-reported health perceptions using existing patient-reported outcome (PRO) measures in THS users, cigarette smokers and former cigarette smokers.

   Endpoints:

   - Scores of the SF-36 assessment (Physical and Mental Health).

5. To evaluate the safety during the study.

   Endpoints:

   - Incidence and frequency of Adverse events (AEs), Serious adverse events (SAEs).

3.3 Exploratory Endpoints

1. To describe the differences in additional BoPH indicative of the multiple mechanistic pathways associated with main smoking-related diseases between THS users, cigarette smokers and former cigarette smokers.

   Endpoints:

   - Inflammation: Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), soluble urokinase Plasminogen Activator Receptor (suPAR),
   - Oxidative stress: Malondialdehyde (MDA).

3.4 Additional Endpoints

The following assessments will be performed as part of the screening procedures or to collect characteristics of the study subjects:

- Physical examination,
- Vital signs,
- Electrocardiogram (ECG),
- Glycated hemoglobin (HbA1c) in blood,
- Questions on tobacco/nicotine-containing products use history,
- Questions on socioeconomic indicators,
- Dietary intake (Qualitative food group frequency questionnaire)
- Lifestyle questionnaire.

3.5 Study Hypotheses and Evaluation Criteria

3.5.1 Hypotheses

The study hypothesis is that there will be favorable differences in three BoPH associated with inflammation, oxidative stress, and arterial stiffness in THS users compared to cigarette smokers.

3.5.2 Evaluation Criteria

Study objectives will be tested in a hierarchical manner:

First, WBC count in blood and 8-epi-$PGF_{2\alpha}$ in urine (expressed as concentration adjusted to creatinine) will be tested as co-primary endpoints using a test-wise type I error level of 5%.

If a statistically significant difference between THS users and cigarette smokers (THS effect) is demonstrated in WBC and 8-epi-$PGF_{2\alpha}$ and the direction of the THS effect observed in the co-primary BoPHs is coherent with the effect observed in the former cigarette smokers group, AIx will be tested using a test-wise type I error level of 5%.

The study will be declared successful if the THS effect is demonstrated either on WBC and 8-epi-$PGF_{2\alpha}$ or on WBC, 8-epi-$PGF_{2\alpha}$, and AIx.

It will not be a requirement that the main analyses are consistently confirmed across the sensitivity analyses or supplementary analysis. The sensitivity and supplementary analyses results will be used to substantiate the credibility of the main analysis.

4 INVESTIGATIONAL PLAN

4.1 Study Design

This is an observational cross-sectional 3-group study with subjects enrolled matched by region, age (< 40, 40-50, > 50 years old), sex, and average daily product consumption over the last year of smoking as self-reported (smoking 10 to 19 cig/day or using 10 to 19 heatsticks/day vs. > 19 cig/day or > 19 heatsticks/day).

The study will be conducted as a multi-center and multi-regional study, in Asia and Europe.

Both regions (Asia, Europe) should have a quota applied to ensure representatives of each constitute at least 40% of the subjects in each group.

Both sexes should have a quota applied to ensure representatives of each constitute at least 40% of the subjects in each group.

A sufficient number of subjects will be screened in order to enroll them into three different groups as follows:

- Approximately 300 current cigarette smokers,
- Approximately 300 THS users with a minimum of one year of THS use,
- Approximately 300 former cigarette smokers with minimum of one year smoking abstinence.

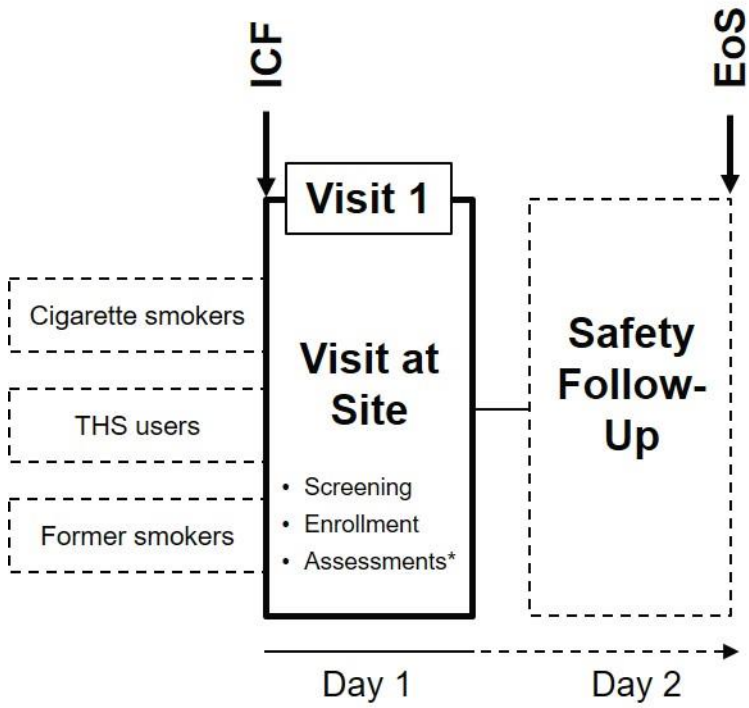

Figure 1 Study Flow Chart

The study will be conducted as follows:

- The Screening/Enrollment/Assessments Visit at Site: Visit 1 (Day 1). This visit will be abbreviated to V1.
- The Safety Follow-up period (Day 2)

The study duration may be extended to maximum 4 days in case of lost to follow-up, including 2 days for additional calls. The EOS of the entire study is the last individual subject's EOS.

Subjects with ongoing AEs at the end of V1 should be contacted at the end of 1-day safety FU period. In case they cannot be reached, two additional attempts at the next 2 consecutive days will be made. If the subjects cannot be reached after the three attempts they will be declared lost to follow-up.

4.2 Selection of Study Population

4.2.1 Inclusion Criteria

The following inclusion criteria will be applicable for this study:

1. Subject is able to understand the information provided in the main ICF and has signed the main ICF.
2. Subject is 30-60 years old.
3. Subject is healthy based on ECG, spirometry, vital signs, physical examination, medical history and Investigator's assessment.
4. Subject is ready to comply with the study procedures.

Cigarette smokers:

5. Has smoked ≥ 10 cigarettes/day on average (no brand restriction) for at least one year prior to screening.
6. Has smoked ≥ 10 cigarettes/day on average (no brand restriction) for at least 10 years.
7. Has not used other tobacco and nicotine products apart from cigarettes on a daily basis over the past year prior to screening.
8. Smoking status will be verified by urinary cotinine test (≥ 200 ng/mL) and CO breath test (≥ 7 ppm).

THS users:

9. Has used ≥ 10 heatsticks/day on average for at least one year prior to screening.
10. Has smoked ≥ 10 cigarettes/day on average (no brand restriction) for at least 9 years prior to switching to THS.
11. Has smoked < 30 cigarettes/month and used other tobacco products or e-cigarettes < daily over the past year prior to screening.
12. Product use will be verified by urinary cotinine test (≥ 200 ng/mL) and CO breath test (< 7 ppm).

Former cigarette smokers:

13. Has not used any tobacco or nicotine products for at least one year prior to screening.
14. Has smoked ≥ 10 cigarettes/day on average (no brand restriction) for at least 9 years prior to stopping smoking.

15. Smoking status will be verified by urinary cotinine test (< 100 ng/mL) and CO breath test (< 7 ppm).

4.2.2 Exclusion Criteria

The following exclusion criteria will be applicable for this study:

1. As per the judgment of the Investigator(s), the subject cannot participate in the study for any reason (e.g., medical, psychiatric and/or social reason). The Investigator should specifically evaluate the subject's eligibility in light of COVID-19 risk factors and local situation.
2. The subject is legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, in a social or sanitary establishment, prisoner or involuntarily incarcerated).
3. The subject has/had clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or conditions that in the opinion of the investigator would jeopardize the safety of the subject or affect the validity of the study results.
4. The subject has abnormal findings on physical examination, in the medical history, deemed clinically significant by investigators.
5. The subject has/had within 30 days prior to screening a body temperature >37.5°C or an acute illness (e.g., upper-respiratory-tract infection, viral infection, etc…) or the subject has confirmed or suspected active COVID-19 infection (based on the signs and symptoms observed at the time of assessment) at screening.
6. The subject has used any prescribed or over-the-counter systemic medication with an impact on primary endpoints within 5 half lives of the medication prior to enrollment in the study (please refer to Appendix B of the protocol).
7. Subject has high blood pressure (hypertension), defined as > 139 mmHg systolic and/or > 89 mmHg diastolic or is currently treated with medication controlling high blood pressure.
8. The subject has (FEV1/FVC) < 0.7 and FEV1 < 80% predicted value at post-bronchodilator (BD) spirometry.
9. The subject has (FEV1/FVC) < 0.75 (pre-BD) and reversibility in FEV1 (that is both > 12% and > 200 mL from pre- to post-BD values).
10. The subject has a history of allergic reactions to salbutamol.
11. The subject has a body mass index (BMI) < 18.5 or ≥ 30 kg/m2.
12. The subject has positive alcohol and/or drug screening test results.
13. The subject has donated or received whole blood or blood products within 3 months prior to V1.

14. The subject has been previously screened for this study.
15. The subject is a current or former employee of the tobacco or e-cigarettes industry or of their first-degree relatives (parent, sibling, and child).
16. The subject is an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, and child).
17. The subject has participated in a clinical study within 3 months prior to V1.
18. For women only: the subject is pregnant (does have a positive pregnancy test) or breast-feeding.

Withdrawals and drop-outs will not be replaced.

4.3 Product Allocation and Blinding

4.3.1 Method of Assigning Subjects to Sequence/Product Arms

Study participants will be assigned to the relevant product use group based on their responses to a pre-screening questionnaire as described below. A urine cotinine and CO breath test will also be used at screening to ensure that the participants are in the correct group.

Potential study participants will be reached through social media and traditional display advertising, such as THS customer database/emailing campaign, and sites' database, as/if approved by Independent Ethics Committee (IEC)/Institutional Review Board (IRB). After registration on the study web platform, they will be asked some questions in an online pre-screening phase about their age, sex, and tobacco/nicotine-containing products use history. Their answers from the online pre-screening will not be recorded in the Case Report Form (CRF). Potential subjects who meet the pre-screening criteria will be invited on site and asked more specific questions about their tobacco/nicotine-containing products use history before enrolment. These answers will be recorded in the CRF.

Current cigarette smokers and former cigarette smokers will be matched with THS users by region, age, sex, and average daily product consumption over the last year of smoking as self-reported during the pre-screening. This will be done using a specifically designed on-line platform. Details of the algorithm being used will be documented elsewhere. For each potential triplet of matched subjects, the THS user will be called first to attend V1, while the current cigarette smoker and former cigarette smoker subjects of the triplet will be retained until THS user has performed V1. Thereafter, the current cigarette smoker and former cigarette smoker will be called to attend V1. If the triplet is incomplete at the time THS user performed V1, all efforts will be done to complete the triplet.

Both regions (Asia, Europe) will have a quota applied to ensure representatives of each constitute at least 40% of the subjects in each group.

Both sexes will have a quota applied to ensure representatives of each constitute at least 40% of the subjects in each group.

4.3.2 Blinding

This is an open-label study; therefore the subjects and Investigators will be unblinded to the subject's group. However, there will be a limited degree of blinding in the data review and data analysis process. In particular, PMI and contract research organization (CRO) personnel will be blinded to the product-use groups, the primary endpoints and other data where values or availability may be indicative of the group allocation, as summarized in Table 1.

Table 1. Description of Blinded Study Personnel

Blinded Study Personnel	Blinded Data[a]	End of Blinding Period
PMI and CRO Study Statisticians	Group for: • All endpoints All data for: • Primary endpoints • Questions on tobacco/nicotine-containing products use history • CO breath test • Cotinine tests • BoExp to HPHCs/nicotine • Inclusion/exclusion criteria • ABOUT–Perceived risk • ABOUT–Dependence	After the SAP finalization or the database lock whichever comes last.
PMI Clinical Scientist		After the SAP finalization or the database lock whichever comes last.

[a] Blinded data will be made accessible to the blinded personnel by means of a dummy group or masking. As part of the PMI quality control (QC) activity, data listings will be reviewed by the CRO and PMI before database lock, with no access to the group information. Full details will be available in the data review plan.

Any PMI and CRO personnel who are not listed in the above table will be unblinded by default.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period (Table 1). PMI will receive blinded and unblinded data for the pre-analysis

data review as planned in the data review plan. Blinded data will be accessible by the blinded study personnel in a masked format or presented independent of the subject identifier so to ensure that data cannot be associated to a subject. Unblinded data will only be reviewed by the unblinded study team.

4.3.3 Compliance to Product Allocation

This is an observational study so subjects are not allocated to a product but assigned a group based on their current product use. The smoking/product use group they are assigned to at Screening will be confirmed by a urine cotinine and CO breath test.

5 DERIVED AND COMPUTED VARIABLES

Reported BMI will be calculated at site from the body weight and height using the following formula:

$$\text{BMI } (\text{kg/m}^2) = \frac{\text{Weight (kg)}}{(\text{height (m)})^2}$$

Waist-to-hip ratio will be calculated at site using the following formula:

$$\text{Waist-to-hip ratio} = \frac{\text{waist measurement in cm}^{(a)}}{\text{hip measurement in cm}^{(a)}}$$

$^{(a)}$rounded to the nearest cm

5.1 Biomarkers

The adjustment of the urinary BoPH and BoExp concentration for Creatinine will be calculated as:

$$\text{Biomarker (corrected for creatinine)} = \frac{[\text{Biomarker}]}{[\text{Creatinine}]}$$

The following biomarkers will be normalized in this manner:

Biomarkers of Potential Harm:

- 8-epi-$PGF_{2\alpha}$ in pg/mg creatinine,

- 11-DTXB2 in pg/mg creatinine.

Biomarkers of Exposure:

- NEQ in mg/g creatinine,
- CEMA in ng/mg creatinine,
- total NNAL in pg/mg creatinine.

5.2 Questionnaires

5.2.1 Questions on Tobacco/Nicotine-containing Products Use History

Subjects will be asked questions about their tobacco and nicotine-containing products use history. They will self-report their tobacco and nicotine-containing product use. The questions will capture key variables of frequency, quantity, intensity, and duration of both exclusive and multiple product use, current and past use, duration of use, duration of interruption, product characteristics, and patterns of use. This information will be used to describe the characteristics of the study subjects and to assess their eligibility for the study.

No scores are derived for this questionnaire.

5.2.2 Lifestyle Questionnaire

The Lifestyle Questionnaire was developed from the Lifestyle Risk Scale and the corresponding study published in 2011 (Alguren and Weitkunat 2011).

The original Lifestyle questionnaire is composed of 9 items and investigates the following risk categories: diet (1 item), alcohol intake (1 item), physical activity (2 items), sleep deficit (1 item), exposure to passive smoking (1 item), smoking (1 item) and BMI (2 items). A modified version of the instrument will be used in the study. The four items related to diet, smoking and BMI will be excluded from this study as these topics are already covered: diet by the Qualitative Food Frequency Questionnaire, smoking by the Product Use History Questionnaire, and BMI by a separate assessment. In addition, the item related to passive smoking will be modified in order to adapt it to all study arms. The trial specific version will consist of 5 items.

The item scaling is dichotomous for the exposure of passive smoking item (item number 5 in the trial specific Lifestyle Questionnaire) and a numerical response is recorded for the rest of the items. A score will be derived for all items, apart from the items on the excluded items on diet, smoking and BMI, using the procedures described in the Lifestyle Questionnaire Scaling

and Scoring Manual v2.0 (See Appendix 13.2). For each item, a higher score indicates higher lifestyle behavior related risk.

A global score will be derived by summing the individual item scores (excluding the item on exposure to passive smoking). For the complete Lifestyle Questionnaire, this gives a score ranging from 0 to 23.2. However, since we are excluding the items on diet, smoking and BMI from this study the score will range from 0 to 11.5. Higher scores indicate higher lifestyle behavior-related health risk.

Item 5 of the trial specific Lifestyle Questionnaire (passive smoking) is not included in the calculation of the global score but will be reported separately as it gives an indication on passive smoking.

5.2.3 Questions on Socioeconomic Indicators

The questions on socioeconomic indicators are used to assess the socioeconomic status (SES) of the subject and cover two socioeconomic metrics, namely perceived financial wellbeing and educational level. Respondents will be asked to answer two questions, one question about the perceived financial welling of their household, and one question about their educational level. Country-specific categories will be provided as response options for the question about the educational level (See Appendix 13.3). For the analysis of this question on educational level, the original variables will be harmonized to regional categories using the EDULVLA 5-level harmonization frame for European countries (incl. Russia). The Asian countries will also be harmonized using the EDULVLA 5-level harmonization frame. Additionally, the participants can select the "prefer not to say" option.

The harmonized regional categories countries are:

1. Less than lower secondary education
2. Lower secondary education
3. Upper secondary education
4. Post-secondary non-tertiary education completed
5. Tertiary education completed

The conversion algorithms can be found in Appendix 13.3.

For perceived financial wellbeing, participants are asked to rate their household's ability to make ends meet using six response options or they can select "prefer not to say". The six

response options of the perceived financial wellbeing will be converted into three groups as follows:

Response options 1 (with great difficulty), 2 (with difficulty), and 3 (with some difficulty) will be classified as low, option 4 (fairly easily) will be classed as moderate and responses 5 (easily) and 6 (very easily) will be classed as high.

5.2.4 Qualitative Food Frequency Questionnaire

The Qualitative Food Frequency Questionnaire was developed by Dehghan et al. (Dehghan, Mente et al. 2012), and it is a generic questionnaire that can be used in multiple countries despite regional differences in intake of a specific food item within a category. It contains all the main food groups, i.e., dairy, meat, fish, fruits and vegetables, and a few food items that are culture dependent such as tofu and soy sauce.

The Qualitative Food Frequency Questionnaire consists of 20 items, where each item represents a different food item. The questionnaire uses the last 12 months as the recall period, and provides response options to indicate the number of times a specific food item was consumed per day, per week, or per month. The frequency of consumption is used for the scoring system. For data analysis, all frequencies of consumption are converted to times per day (for example, a response of 3 servings per week is converted to 0.43 servings per day). The following conversions will be used to convert to times per day:

- Number of times per week will be divided by 7
- Number of times per month will be divided by 30

5.2.5 ABOUT–Perceived Risk

Risk perception is a key factor driving tobacco product uptake, use and cessation. As part of the ABOUT Toolbox (Chrea, Acquadro et al. 2018), the ABOUT–Perceived Risk (Salzberger, Chrea et al. 2017, Cano, Chrea et al. 2018) was developed as a self-report measure designed to assess the perceived risks associated with the use of tobacco and nicotine-containing products (TNPs), including cigarettes, nicotine replacement therapy products (NRTs), and

reduced risk products (RRPs). The ABOUT–Perceived Risk can also be used to assess the perceived risks associated with the cessation or the past use of cigarettes.

The ABOUT–Perceived Risk questionnaire consists of three domains/scales: Perceived Health Risk scale, Perceived Addiction Risk scale, and two single items on Perceived Harm to Others. For this study, only the 9-item short version of the Perceived Health Risk scale will be assessed in order to reduce response burden and since it is applicable for assessing group means rather than individual measures.

The questionnaire will be self-administered to all subjects as follows:

- THS users (to assess perceived personal risk of THS as current users of the product and perceived personal risk of cigarettes as former cigarette smokers)
- Cigarette smokers (to assess perceived personal risk of cigarettes as current cigarette smokers and perceived general risk of THS)
- Former cigarette smokers (to assess perceived personal risk of cigarettes as former cigarette smokers and perceived general risk of THS).

Responses are measured on a 5-point Likert-like scale (0=no risk; 1=low risk; 2=moderate risk; 3=high risk; 4=very high risk). An "I don't know" response option is also possible for each item. "Don't know" responses to items and skipped items are interpreted as missing data. If a participant presents more than 50% of the items within a scale for which data is missing, then a total scale score is not provided for this participant. See section 9.1.6.2.1 for further details on handling missing data for the ABOUT-Perceived Risk.

A summary measure will be derived based on the scoring guidelines provided in ABOUT-Perceived Risk User Manual Edition 2 [8]. The responses for each of the items will be added up to produce a total raw score. Then the conversion table below (Table 2) will be used to derive the corresponding person measure which represents, for that participant, the level of Perceived Health Risk associated with the product the scale has been applied to. Therefore, the transformed total score will range from 0 (no perceived risk) to 100 (very high perceived risk).

Table 2. ABOUT™—Perceived Risk - Perceived Health Risk (9-item scale) – Sum Score to Measure Conversion

Sum Score (9-items)	Participant Measure (Transformed to 0 to 100 scale)
0	0
1	10
2	15
3	18

4	21
5	24
6	26
7	28
8	31
9	33
10	35
11	38
12	40
13	42
14	44
15	46
16	48
17	49
18	51
19	53
20	55
21	57
22	59
23	60
24	62
25	64
26	65
27	67
28	69
29	70
30	72
31	74
32	77
33	79
34	83
35	87
36	100

5.2.6 ABOUT–Dependence

The ABOUT–Dependence is part of the ABOUT™ Toolbox (Chrea, Acquadro et al. 2018), and was developed to provide a measure of perceived psychological dependence associated with the use of different TNPs and across exclusive and multiple TNPs users (Chrea,

Salzberger et al. 2019). The measure has been validated in a diverse population of TNP users which included exclusive and multiple TNP users across different products such as cigarettes, electronic nicotine delivery devices (e.g., e-cigarettes), smokeless tobacco, cigars/cigarillos, waterpipes, pipes, and nicotine replacement therapies (NRTs). Inclusion of the ABOUT−Dependence in this study will provide further data for validation in users of heated tobacco products such as THS.

The self-administered 12-item measure consists of three main perceived dependence domains: Extent of use (2 items) referring to the timing of use (time to first product use, time from last product use to going to bed), Signs and Symptoms (5 items) which captures the feelings and experience of the symptoms of perceived dependence, and Behavioral Impact (5 items) which captures the behavioral aspects of perceived dependence and impact on daily activities. Separate scores for each domain and a total score will be calculated as outlined in the ABOUT-Dependence User Manual Edition 2 [9]. Details are provided below.

A 6-point Likert-type scale is used for the Extent of use domain to indicate increasing severity; the scoring of items 1 and 2 is:

0 = “more than 3 hours”;

1 = “more than 1 hour to 3 hours”;

2 = “31 to 60 minutes”;

3 = “16 to 30 minutes”;

4 = “6 to 15 minutes”;

5 = “0 to 5 minutes”

The Extent of use domain total raw score is derived by summing the scores for the two items. This provides a minimum of 0 and maximum of 10 for the Extent of use domain total raw score.

A 5-point Likert-type scale is applied for the other two Signs and Symptoms and Behavioral Impact domains to indicate increasing severity of perceived dependence.

For items 3a and 3b, the scoring of items is as follows:

0 = “Not at all”;

1 = “A little” ;

2 = “Moderately”;

3 = “Very much”;

4 = “Extremely”.

For items 4a, 4b, 4c, 4d, 4f, 4g, and 4h, the scoring of items ranges from:

0 = "Never";

1 = "Rarely";

2 = "Sometimes";

3 = "Most of the time";

4 = "All the time".

Domain total raw scores will be derived by summing the scores for each item within that domain. This produces a minimum of 0 and a maximum of 20 for the Signs and Symptoms domain total raw score and for the Behavioral Impact domain total raw score, respectively.

The domains and the scoring procedures for each domain are summarized in Table 3.

Table 3. About-Dependence Domain and Scoring Details

Domain	Items	Individual Item Scores	Domain Total Raw Score
Extent of use	Item 1: how soon after woke up used first product Item 2: how long before going to sleep used last product	A 6-point Likert-scale ranging from 0 to 5.	Item 1 + Item 2 Range: 0 to 10 Higher scores indicate higher severity/perceived dependence
Signs and Symptoms	Item 3a need to function "normally" Item 3b difficult to completely quit Item 4a strong desire to use Item 4c had to have one	5-point Likert scale ranging from 0 to 4.	Item 3a + Item 3b + Item 4a + Item 4c + Item 4e Range: 0 to 20 Higher scores indicate higher severity/perceived dependence

	Item 4e hard to control the need or urge		
Behavioral Impact	Item 4b use more than intended Item 4d use in situations not supposed to Item 4f sneak off to use Item 4g avoid an activity Item 4h stop what doing to use	5-point Likert scale ranging from 0 to 4.	Item 4b + Item 4d + Item 4f + Item 4g + Item 4h Range: 0 to 20 Higher scores indicate higher severity/perceived dependence

The domain scores will be transformed to a 0-100 scale using the transformation described in the ABOUT-Dependence User Manual Edition 2.

A total composite score from all the 12-items across the three domains will also be calculated. Subject raw scores will be transformed using conversion tables to provide a total measure score (ranging from 0 (no perceived dependence) to 100 (very high perceived dependence). The following conversion to be applied can be found in Table 4. This has been taken from Table 6 in the User Manual, using the transformations for the "Exclusive users of either Cigarettes, Smokeless tobacco, Pipe, or NRTs" column.

Table 4. About – Dependence Composite Score Transformation

Composite raw score (complete data)	Measure score (transformed 0-to-100 scale)
0	0
1	16
2	22
3	27
4	30
5	32
6	35
7	36

8	38
9	40
10	41
11	43
12	44
13	45
14	47
15	48
16	49
17	50
18	51
19	52
20	53
21	54
22	55
23	55
24	56
25	57
26	58
27	59
28	59
29	60
30	61
31	61
32	62
33	63
34	63
35	64
36	65
37	65
38	66
39	67
40	68
41	68
42	69
43	70
44	71
45	73
46	75
47	77
48	80
49	86

50	100

This questionnaire will be administered for assessment and comparison of self-reported perceived dependence in subjects in the current THS user and current cigarette smoker groups.

Further details of the scoring can be found in the ABOUT-Dependence User Manual Edition 2 [9].

Methods for handling missing data when deriving the scores for the ABOUT-Dependence Questionnaire are detailed in Section 9.1.6.2.2.

5.2.7 36-Item Short Form Health Survey (SF-36)

The SF-36 was developed to measure generic health concepts relevant across age, disease, and treatment groups. It consists of 36 items, covering the following domains: Physical Functioning (PF) (10 items), Role-Physical (RP) (4 items), Bodily Pain (BP) (2 items), General Health (GH) (5 items), Vitality (VT) (4 items), Social Functioning (SF) (2 items), Role-Emotional (RE) (3 items), Mental Health (MH) (5 items), and an additional item on Reported Health Transition (perceived change in health). The response options include dichotomous and 5 to 6-point Likert Scales.

All items, domain scores and summary measures are scored so that a higher score indicates a better health state. Norm-based scores by domain and Physical Component Summary (PCS) and Mental Component Summary (MCS) scores will be derived based on the guidelines provided in the User's Manual for the SF-36v2® Health Survey. 2nd ed, (Ware, M. et al. 2017).

5.2.8 Assessment of Cough

Subjects will be asked if they have experienced a regular need to cough (e.g., whether they have coughed several times in the previous 24 hours prior to assessment). If the answer is ‘yes’, subjects will be asked to complete a Visual Analogue Scale (VAS) on cough impact and three individual questions on cough intensity, cough frequency, and sputum production.

On the VAS, subjects will assess how bothersome their cough is ranging from “not bothering me at all” to “extremely bothersome”. This will give a numeric value between 0 and 100, measured on a 100 mm scale.

Responses to the three individual questions on cough intensity, cough frequency and sputum production will be captured with Likert scales as shown in Table 5.

Table 5. Cough Assessment Scale Details

Question	Likert Scale
1. Intensity of cough	1= very mild 2 = mild 3 = moderate 4 = severe 5 = very severe
2. Frequency of cough	1= rarely 2 = sometime 3 = fairly often 4 = often 5 = almost always
3. Amount of sputum production	0 = no sputum 1= moderate amount 2 = a larger amount 3 = a very large amount

For the calculation of the summary statistics for subjects reporting no regular need to cough, cough impact will be imputed as 0 and the intensity of cough, the frequency of cough, and the amount of sputum will be imputed as 0 ("No regular cough").

5.3 Categorical Variables

The categorical variables used in this study are shown below (Table 6). Additional categorical variables used for stratification are reported in Section 9.1.1.

Table 6. Categorical Variable Definitions

Variable	Categories	Details
Age	<40 40 – 50 >50	Matching variable and Stratification Variable
Sex	Female Male	Matching variable and Stratification Variable
BMI (kg/m^2)	Normal ≥ 18.5 and < 25.0 Overweight ≥ 25.0 and < 30.0 Note that patients with BMI <18.5 (underweight) and ≥ 30 (Obese) are excluded from the study as per the inclusion/exclusion criteria.	Derived
Region	Asia Europe	Matching variable and Stratification Variable
Average Daily Product Consumption	Smokers: 10 to 19 cig/day >19 cig/day THS Users: 10 to 19 heatsticks/day >19 heatsticks/day	Matching variable and Stratification Variable
Tobacco/nicotine-containing products use history	<10 pack-year 10 to 20 pack-year >20 pack-year	Derived Stratification Variable
Time since quitting/switching	≤2 years >2 years	Derived Stratification Variable
Adverse event severity	Mild Moderate Severe	Recorded in CRF

Adverse event relationship to study procedures	Related Not related	Recorded in CRF
Outcome of adverse event	Fatal Not recovered/not resolved Recovering/resolving Recovered/resolved Recovered/resolved with sequelae Unknown	Recorded in CRF
Seriousness Criteria	Fatal Life-Threatening Requires hospitalization Results in disability/incapacity Congenital anomaly/birth defect Important Medical Event	Recorded in CRF

5.4 Safety Data Derivations

Prior medication is defined as any medication that started and ended prior to Screening.

Concomitant medication is defined as any medication starting on or after Screening. Medications that started prior to screening and are ongoing at Screening are also considered as concomitant.

6 SAMPLE SIZE JUSTIFICATION

A sample size of 300 cigarette smokers and 300 THS users will provide more than 80% power to detect a favorable effect on WBC and 8-epi-$PGF_{2\alpha}$ using as assumptions the observed effects in a cross-study analysis at the 6 month timepoint (report on file) of two clinical studies ZRHR-ERS-09-US (Philip Morris Products S.A.) and SA-SCR-01 (Philip Morris Products S.A.). ZRHR-ERS-09-US was a 2-arm randomized study in which adult healthy smoking subjects were asked to switch to THS or to continue smoking their own brand of cigarettes for 6 months. In the SA-SCR-01 study, the same parameters were assessed in adult healthy cigarette smokers who were asked to quit smoking for 12 months.

In the above mentioned cross-study analysis, the following levels were observed in WBC and 8-epi-$PGF_{2\alpha}$ that formed the assumptions for the sample size calculation in this study:

WBC (GI/L):

- THS: n=93, LS Mean = 6.61, 95%CI = 6.26, 6.96.
- CC: n=364, LS Mean = 7.36, 95%CI = 7.18, 7.54.

8-epi-$PGF_{2\alpha}$ (pg/mg creat):

- THS: n=92, Geometric LS Mean = 249, 95%CI = 226, 276.
- CC: n=359, Geometric LS Mean = 319, 95%CI = 302, 337.

120 evaluable subjects per group were determined sufficient to demonstrate with respectively 90% and 95% power, more than 80% overall, significant differences between the two groups on WBC and 8-epi-$PGF_{2\alpha}$.

Planned sample size accounts for a multi-regional differential effect on BoPH that was observed in the SA-SCR-01 study and a potential mis-self-reporting of product use.

7 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There are no changes from the protocol specified analyses.

8 ANALYSIS SETS

The analysis sets of interest are:

- Full Analysis Set (FAS).
- Per-Protocol (PP) Analysis Set.

8.1 Full Analysis Set (FAS)

The FAS will be composed of all subjects attending V1.

8.2 Per Protocol Analysis Set (PP)

The PP Analysis Set will be a subset of the FAS and will exclude subjects with deviations impacting the evaluability of the primary objective.

Protocol deviations are defined in Section 8.3. Deviations that will lead to exclusion from the PP population will be defined prior to database lock and finalized at a blinded data review meeting. See Section 8.3 for definitions of deviations.

8.3 Protocol Deviations

Protocol deviations are defined as deviations from the study procedures as defined in this document, including but not limited to any violation of inclusion/exclusion criteria, assessments not performed or performed outside the scheduled time windows, or use of drugs that are known to affect primary endpoints (Listed in Appendix B of the Protocol). Protocol deviations will be classified as minor/major. Major deviations will be further reviewed to determine whether or not they may impact the evaluability of the result and should therefore lead to the subject being excluded from the PP Analysis Set.

All protocol deviations will be documented in the clinical trial management system (CTMS) or other approved format and will be reviewed periodically to identify trends to improve monitoring and/or potential impact on the statistical analysis.

8.3.1 Major Protocol Deviations

Subjects with major deviations will be identified to determine if they will be excluded from the PP Analysis Set. This will take place in the data review meeting prior to database lock. The categories for major deviations will include (but are not limited to) the categories outlined in Table 7.

Table 7. Definitions of Major Protocol Deviations

Category	Description
Product mis-assignment	Urine cotinine/CO breath test suggests subject is not in the product use group assigned at Screening
Mis-stratification	Subject data suggests they are not in the stratification group assigned at screening
Primary Endpoint Assessment Missing	Subject has a missing value for WBC, 8-epi-$PGF_{2\alpha}$ or AIx at V1.

Violation of Inclusion/Exclusion Criteria	Violations of inclusion criteria will be assessed for their impact on the PP Analysis Set
Use of drugs known to affect the primary endpoint	Subjects with prior/concomitant medications listed in the table in Appendix B of the protocol and with a last dose closer to the measurement of WBC or 8-epi-$PGF_{2\alpha}$ than indicated in this table.
Dietary restrictions not met	Subject does not follow the dietary restrictions outlined in the protocol

8.3.2 Minor Protocol Deviations

Categories for minor protocol deviations will include (but are not limited to) those defined in Table 8.

Table 8. Definitions of Minor Protocol Deviations

Category	**Description**
Concomitant Medication	Prior/concomitant medication not listed in Appendix B of the protocol
Violations of inclusion/exclusion criteria	Violations of inclusion/exclusion criteria not considered major deviations.
Other Assessment Missing	Assessment other than WBC, 8-epi-$PGF_{2\alpha}$ or AIx missing
Safety follow-up visit not completed	Safety follow-up on day 2 not completed.
Assessment not in correct order	AIx, PWV and FMD assessments should be performed at least 2 hours after having stopped smoking/using THS and 3 hours after consuming a large meal and/or caffeine-containing food/drinks.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

9.1.1 Stratified Presentation

For further describing WBC, 8-epi-$PGF_{2\alpha}$, AIx, BoPH indicative of the multiple mechanistic pathways associated with main smoking-related diseases and BoExp to HPHCs and nicotine, the following stratification criteria will be used:

1. Age (< 40, 40-50, > 50 years old),
2. Sex (Female, Male),
3. Average daily product consumption over the last year (smoking 10 to 19 cig/day or using 10 to 19 heatsticks/day vs. > 19 cig/day or > 19 heatsticks/day),
4. Region (Asia, Europe),
5. Tobacco products use history (<=10, >10 pack-years),
6. Time since quitting/switching (<=2, >2 years),

9.1.2 Sub-group Analyses

No further sub-group analyses are planned.

9.1.3 Listings

All data from primary endpoints (Section 3.1), secondary endpoints (Section 3.2), exploratory endpoints (Section 3.3), and additional endpoints (Section 3.4) will be presented in listings, ordered by group, subject, and study day unless specified otherwise.

9.1.4 Descriptive Statistics

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum, maximum; for log-normal data the geometric mean and geometric coefficient of variation (CV) will be presented instead of the arithmetic mean and SD. Minimum and maximum will be presented to the same precision as the raw data; Mean, median, quartiles and confidence intervals will be presented to 1 more

decimal place than the raw data and SD will be presented to 2 more decimal places. CV will be presented to 1 decimal place.

For categorical variables frequency counts (n) and percentages (%) will be presented. The number and percentage of subjects with missing data will also be presented, as well as the number and percentage of subjects with not evaluable data (if applicable).

If the total number of items/events is zero, any further breakdown into sub-categories will not be presented.

Unless specified otherwise the denominator for percentages will be the total number of subjects in each respective group except missing and not evaluable data.

All percentages will be presented to one decimal place, except as follows

- Percentages = 100, will be presented as "100%" (no decimal places)
- Percentages < 0.1, will be presented as "<0.1%"
- Percentages for a 0 count, will not be presented.

The following product use group labels will be used throughout the TFLs:

Product Use group	Format	Order in TFLs
Current Cigarette Smoker	Current Smoker	1
Tobacco Heating System User	THS User	2
Former Cigarette Smoker	Former Smoker	3

9.1.5 Definitions for Statistical Data Analysis

At the time of the present protocol, no new terms are defined.

9.1.6 Handling of Dropouts or Missing Data

9.1.6.1 Laboratory Parameters

Values below the lower limit of quantification (LLOQ) will be imputed using LLOQ/2. For values above the upper limit of quantification (ULOQ), the ULOQ will be imputed.

The number of values below LLOQ or above ULOQ will be presented in each summary table. If 50% or more data are below LLOQ or above ULOQ, only the number (%) of values below LLOQ or above ULOQ will be reported in the summaries, together with minimum and maximum of the observed values.

9.1.6.2 Questionnaires

9.1.6.2.1 ABOUT – Perceived Risk

Missing data will be handled according to the ABOUT-Perceived Risk User Manual Edition 2 [8].

If there is less than 50% within-person item-level missing data (i.e. if a subject has a non-missing response for at least 5 of the questions), use the following rule to produce a complete within-person response pattern:

1. Sum the available within-person item responses and divide that score by the number of items which have responses.

2. Replace the items with missing responses with the within-person mean.

3. Calculate a sum total score by summing all 9 items and round to the nearest whole integer.

4. Use the conversion table in Section 5.2.5 (Table 2) to derive the corresponding person measure.

9.1.6.2.2 ABOUT - Dependence

Missing data will be handled according to the ABOUT-Dependence User Manual Edition 2 [10]. If there is one item of missing data in the Signs and Symptoms or Behavioral Impact domain, the following rule will be used to derive the domain total raw score:

1. Substitute the average raw score of the four non-missing items for the missing item value.

2. Calculate a sum total score for the domain and round to the nearest whole integer.

3. Use the applicable conversion table from the User Manual to derive the corresponding measure score.

Where two or more items are missing from the Signs and Symptoms or Behavioral Impact domain or any one of the items in the Extent of use domain is missing, the domain total raw score will not be calculated or imputed and will be set to missing for that subject.

For the composite raw score, in cases where there is one missing item in the Signs and symptoms or Behavioral impact domain, the following rule will be applied:

1. Substitute the average raw score of the four non-missing items for the missing item value in each domain (Signs and symptoms or Behavioral impact)

2. Calculate a sum total score for the 12 items of the instrument and round to the nearest whole integer.

3. Use the conversion Table 4 to derive the corresponding measure score.

Where two or more items are missing from the Signs and symptoms or Behavioral impact domain or any one of the items in the Extent of use domain is missing, the composite raw score will not be calculated or imputed in this way. In that case, the composite score from the individual will be set to missing.

9.1.6.3 Missing or Partial Dates

Missing or partial dates will not be imputed for AEs, medical history and concomitant medications, but the following assumptions will be made in order to assign them to categories:

Date Information	AE Category	Disease Category	Medication Category
If the date is completely missing or for partial dates, if the month/year is the same as, or later than the month and/or year of screening	NA	Concomitant Disease	Concomitant Medication
For partial dates, if the month/year is earlier than the month and/ or year of screening	NA	Medical History	Prior Medication

9.1.6.4 Insufficient Data for Analysis/Presentation

Some of the TFLs will not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No adverse events related to study procedures occurred for this study".

If there are no values or events for a planned output then related outputs will not be presented. For example, if the number of AEs related to the study procedure is zero then the presentation by severity of related adverse events will not be produced.

Subgroup outputs for AEs will only be presented if there are sufficient numbers of AEs.

9.1.7 Handling of Unplanned Data

Since most of the data collection only occurs over one day, unplanned data is not anticipated. However, if any unscheduled assessments do occur, they will be included in listings only and only scheduled assessments will be summarized.

9.1.8 Multiple Comparison/Multiplicity

The overall, study-wise, type I error will be preserved at 5% two-sided by simultaneously testing WBC and 8-epi-$PGF_{2\alpha}$ at a 2.5% one-sided test-wise alpha level and testing AIx, in a hierarchical approach, at a 2.5% one-sided test-wise alpha level only if both WBC and 8-epi-$PGF_{2\alpha}$ have reached statistical significance.

Unless stated otherwise, for other analyses the statistical tests are two-sided and are conducted at the 5% level, and all quoted confidence intervals (CIs) are two-sided 95% CIs.

No multiplicity adjustments will be made for the secondary objectives.

9.1.9 Multicenter Studies

This is a multi-center study. Unless specified otherwise, summaries will pool data from all centers.

9.2 Disposition of Subjects

Subject disposition will be summarized by absolute counts (n) and percentages (%) and split by each arm including counts for all subjects. Percentages will be based on the number of

subjects in each smoking group. Counts and percentages of the number of subjects enrolled in the study, the number of subjects who completed the study, the number of subjects who prematurely discontinued, and primary reason for withdrawal will be displayed.

Separate summaries will also be conducted by country/center.

9.3 Demographic and Other Baseline Characteristics

Demographic data will be summarized by group (including a total column) according to Section 9.1.3. The following variables will be included: Age (years), age group (see section 9.1.1), sex, race, height (cm), weight (kg), waist to hip ratio, BMI (kg/m2), HbA1c (mmol/mol), SES, smoking intensity (pack-years). Separate summaries will also be conducted by the stratification criteria described in Section 9.1.1 for the FAS population and PP Analysis Set.

9.4 Measurement of Product Compliance

Not Applicable.

9.5 Extent of Exposure (Product Consumption)

Not Applicable.

9.6 Planned Statistical Analyses

9.6.1 Primary Estimand

The primary estimand of the primary objective (Section 3.1**Error! Reference source not found.**) is defined by the following components:

- **Product Use Under Evaluation**: The regular and predominant use of the Tobacco Heating System for at least one year. The use of other tobacco or nicotine product being very limited or inexistent (further defined per relevant inclusion criteria in Section 4.2.1).
- **Target Population**: The target population is defined as the Per-Protocol Analysis Population and the relevant inclusion/exclusion criteria in Sections 4.2.1 and 4.2.2), notably defined by healthy adult subjects, 30 – 60 years old who have smoked at least 10 cigarettes a day for at least 9 years and who have not used other tobacco or nicotine products during this period.

- **Variables of interest**:
  - WBC in blood,
  - 8-epi-$PGF_{2\alpha}$ in urine (expressed as concentration adjusted to creatinine),
  - AIx
- **Intercurrent Events**:

Note that these intercurrent events apply to all three of the primary endpoints.

  - Non-adherence to product use is handled through inclusion criteria as defined in Section 4.2.1 and notably self-reported product use, cotinine test, and CO breath test
    - The main analysis based on the PP Analysis Set will use the While on Treatment Strategy and impacted observations on the variable of interest will be ignored.
  - Other analysis based on the FAS will use the Treatment Policy Strategy and observations on the variable of interest will be used if they exist.
  - Discontinuations and Missing Data are not expected to be associated with study groups or endpoints and are unlikely given the 2 days duration of this cross-sectional study. Discontinuation effect and missing data will be ignored.
  - Concomitant medications, physical conditions and disease that could potentially impact the level of the variable of interest are handled through exclusion criteria as defined in section 4.2.2. The same strategy as described for non-adherence will be used.

- **Population-Level Summary**:
  - The mean difference of WBC in blood at Day 1 between THS user and cigarette smokers.
  - The geometric mean ratio of 8-epi-$PGF_{2\alpha}$ in urine (expressed as concentration adjusted to creatinine) at Day 1, between THS user and cigarette smokers.
  - The mean difference in AIx at Day 1 between THS user and cigarette smokers.

9.6.1.1 Main Analysis

The PP Analysis Set will be used for the primary analysis.

Endpoints related to the primary objective will be summarized at V1 for the PP Analysis Set, for cigarette smokers, THS users, and former smokers. Further descriptive statistical summaries will be performed by the stratification criteria described in section 9.1.1.

Comparisons will be made between THS users and cigarette smokers:

- The statistical analysis will be performed on the regular scale for WBC and AIx and on the natural log scale for 8-epi-$PGF_{2\alpha}$ using generalized linear mixed models adjusting for the matching variables (region, age, sex, and the self-reported average daily product consumption over the last year of smoking), the interaction between product use group and the self-reported average daily product consumption over the last year of smoking, and study site as a random effect.

- The least squares (LS) means will be presented for THS users and cigarette smokers along with the difference (THS Users – cigarette smokers) or (if the biomarker is log transformed) ratio (THS Users: cigarette smokers), the associated two-sided 95% CI and a one-sided p-value.

- The direction of the one-sided test will be determined from the comparison between former smokers and cigarette smokers (detailed in Section 9.6.1.3)

- Due to the cross-sectional design of the study, missing data are unlikely to occur but if they do they are likely missing completely at random. Therefore, no imputation for missing data will be performed.

- Analysis of residuals (model diagnostics) and comparison between the values predicted versus the observed endpoint values (calibration) will be reported.

9.6.1.2 Sensitivity Analyses

Modelling assumptions from the main analysis will be evaluated and model fit assessed by the analysis of residuals (model diagnostics) and by comparing the values predicted versus the observed endpoint values (calibration). The biomarkers will be transformed to the log-scale if there appears to be evidence of non-normality. If there are still issues with the normality assumption after the log transformation alternative non-parametric methods will be explored.

Irrespective of the results of the residuals analysis, WBC will additionally be analyzed in the same manner as described for the main analysis, but transformed to the natural log scale.

For all the sensitivity (described in this section) and supplementary analyses (described in Section 9.6.1.3):

- The least squares (LS) means on the original scale, along with the associated two-sided 95% CI on the original scale and the two-sided p-value, will be presented for product use groups and contrasts between product use group.
- For contrasts performed on endpoints using their un-transformed values the negative term will be related to the cigarette smokers, while for contrasts performed on endpoints using their values on the natural log-scale the denominator will be related to the cigarette smokers.
- Analysis of residuals (model diagnostics) and comparison between the values predicted versus the observed endpoint values (calibration) will be reported.
- Forest plots of the results will also be presented by endpoints, by analysis set and by statistical model.

9.6.1.3 Supplementary Analysis

- The main analysis (Section 9.6.1.1) and the sensitivity analyses (Section 9.6.1.2) will be additionally performed at V1 for the FAS.

The Supplementary Analyses described below will be performed for the FAS and the PP analysis sets.

- Potential predictors of effect or confounders will be investigated for each of the primary endpoints by repeating the main analyses outlined in Section 9.6.1.1 and additionally including these predictors of effect and confounders in a stepwise regression model with an entry significance level of 0.15 and stay significance level of 0.05. The following potential predictors of effect and confounders will be considered:
    - The interaction between product use group and the natural log time (in years) in the product use group (time since quitting/switching/smoking),
    - Perceived financial wellbeing,
    - Educational level,
    - BMI
    - Level of HbA1c
- The main analysis will be repeated for each primary endpoint stratified by the level of HbA1c (<6.5% and >=6.5%)

- To define the directionality of the one-sided test performed in the main analysis (Section 9.6.1.1), an analysis as described for the main analysis will be performed with the exception that former smokers will be compared with cigarette smokers for the 3 co-primary BoPHs.
    - Using generalized linear mixed models adjusting for the matching variables (region, age, sex, and the self-reported average daily product consumption over the last year of smoking), the interaction between product use group and the self-reported average daily product consumption over the last year of smoking, and study site as a random effect.
    - The least squares (LS) means will be presented for former smokers and cigarette smokers along with the difference (former smokers – cigarette smokers) or (if the biomarker is log transformed) ratio (former smokers: cigarette smokers), the associated two-sided 95% CI and a two-sided p-value.
    - Modeling assumptions will be evaluated and model fit assessed by the analysis of residuals (model diagnostics) and by comparing the values predicted versus the observed endpoint values (calibration).
- To overcome potential issue of multi-collinearity, whilst also ensuring balanced distributions over our matched variables, inverse probability weighted model using the logit of the propensity score will be fitted:
    - The propensity score will adjust:
        - For the matched variables: region, age, sex, and the self-reported average daily product consumption over the last year of smoking, and
        - For potential confounders: perceived financial wellbeing, and educational level, BMI, stratified level of HbA1c (<6.5% and >= 6.5%)
    - Using the logit of the propensity score, weights for the average treatment effect on the "treated" (ATT) will be determined for the 3 groups. THS users group being the reference (the “treated”), using the following method:
        - The weight of THS users will be 1,
        - The weight of cigarettes smokers will be determined using the standard method including only THS users and cigarettes smokers, and

- The weight of former smokers will be determined using the standard method including only THS users and former smokers

- The propensity score model will include all the subjects from the analysis set of interest (PP or FAS) independently from patients' availability of the data for the endpoints of interest.

- Balance diagnostics will be assessed for the logit of the propensity score and each variable by looking at the standardized mean difference (SMD) between the exposure groups analyzed. Results will be reported for both before (unweighted) and after propensity score weighting.

- Weights will be applied to a generalized linear mixed model using robust covariance estimators, adjusting for product use and study site as a random effect. The classical sandwich estimator will be used by specifying the empirical=classical option in proc GLIMMIX. If any predictors of effect or confounders ($p<0.05$) is identified in section 9.6.1.1 or 9.6.1.2 then these will be adjusted for here, so that the model is doubly robust.

- Comparisons will be made between THS users and cigarettes smokers, and between former smokers and cigarettes smokers.

9.6.2 Secondary Analyses

Unless otherwise specified, for secondary analysis:

- All the descriptive and inferential analysis will be performed in the FAS and the PP Analysis Set.
- Endpoints will be summarized at V1 as described in section (9.1.4) by groups and further descriptive statistical summaries will be performed by the stratification criteria described in section 9.1.1.
- For continuous variables,

  - The hypothesis to be tested is that the (geometric) mean level for THS users or former cigarette smokers is different from the (geometric) mean level for current smokers.

  - Tests will be conducted using the same methodology as described in section 9.6.1.1. and in addition, the same methodology as described in section 9.6.1.3 using (ATT) propensity score weighting.

- The least squares (LS) means will be presented by groups and along with group difference (or if the biomarker is log transformed, the group ratio), along with the associated two-sided 95% CI and a two-sided p-value.
    - Evaluated differences will be reported as THS users – cigarette smokers, and former smokers – cigarette smokers
    - Evaluated ratios will be reported as THS users: cigarette smokers and former smokers: cigarette smokers

- Analysis of residuals (model diagnostics) and comparison between the values predicted versus the observed endpoint values (calibration) will be reported.
- If applicable, forest plots of the results will also be presented by endpoints, by analysis set and by weighting approach (unweighted, or ATT propensity score weighting)

9.6.2.1 Secondary Endpoint 1

The BoPH indicative of the multiple mechanistic pathways associated with main smoking-related diseases will be described as continuous variables and analyzed, using the same methodology as outlined in 9.6.1.1:

- Fibrinogen, HCY, hs-CRP, MPO, 11-DTXB2, FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, sICAM-1, PWV, TC, and TG will be analyzed on the natural log-scale.
- HDL-C, LDL-C, ox-LDL, FMD will not be transformed prior to analysis.

The endpoints related to the assessment of cough:

- Will be summarized:
    - As categorical variables for intensity of cough, frequency of cough, and amount of sputum production (from the Cough Questionnaire) as well as the answer to the question if subject has experienced regular need to cough, and
    - As continuous variables (using the same methodology as outlined in 9.6.1.1) for the cough impact (VAS), and
- Will be tested using an unweighted approach and a weighted approach as described in section 9.6.1.3 using (ATT) propensity score weighting:

- Using a Cochran-Mantel-Haenszel (CMH) test for intensity of cough, frequency of cough, and amount of sputum production to evaluate a row mean score difference and the related 2-sided p-values. Subjects with no regular cough will be imputed to 0. The models will be stratified for matching variables,

- A logistic regression model for the regular need to cough question, to evaluate the odds ratio of regularly coughing, the related 95% CI and 2-sided p-values will be reported.

    - For the unweighted approach, the models will include terms for matching variables and study site as a random effect, and

    - For the weighted approach, the model will include in addition to the matching variables and study site as a random effect, the potential predictor of effect or confounders using a stepwise regression analysis as described in Section 9.6.1.2.

- A logistic regression model for the cough impact (VAS) that will be categorized (≤20, and >20), similar to the model described for the regular need to cough question.

9.6.2.2 Secondary Endpoint 2

The levels of BoExp to HPHCs and nicotine (COHb, total NNAL, NEQ, CEMA) will be described as continuous variable and analyzed on the natural log scale using the same methodology as outlined in 9.6.1.1.

9.6.2.3 Secondary Endpoint 3

The transformed domain scores and the total measure score from the ABOUT – Dependence questionnaire and the ABOUT – Perceived Risk questionnaire will be summarized as continuous variables.

The transformed domain scores from the ABOUT – Dependence questionnaire and the ABOUT – Perceived Risk questionnaire will be analyzed using the same methodology as outlined in 9.6.1.1.

The transformed domain scores from the ABOUT – Dependence questionnaire will be compared only between THS users and cigarette smokers only, since this questionnaire is not applicable to former smokers.

9.6.2.4 Secondary Endpoint 4

The norm-based scores of SF-36 individual domains, as well as PCS and MCS components will be summarized as continuous variables.

The norm-based scores of PCS and MCS components will be analyzed using the same methodology as outlined in 9.6.1.1.

9.6.3 Exploratory Analyses

Exploratory Analysis will be performed as Secondary Analysis described in section 9.6.2.

The levels of the additional BoPH indicative of multiple mechanistic pathways associated with main smoking-related diseases (IL-6, TNF-α, suPAR, MDA) will be summarized as continuous variables and analyzed on a natural log scale using the same methodology as outlined in 9.6.1.1.

9.6.4 Additional Analyses

- Physical examination will be summarized as described in Section 9.6.6.3.
- Vital signs data will be summarized as described in Section 9.6.6.4.
- ECG data will be summarized as described in Section 9.6.6.6.
- HbA1c is summarized with the demographic and baseline characteristics as described in Section 9.3.
- Questions on tobacco/nicotine-containing products use history will be summarized at V1.
- Questions on socioeconomic indicators will be summarized as categorical variables for the FAS and PP Analysis Set, for each product use group at V1 as described in section 9.1.4.
- Items per day for each of the items recorded in the Qualitative Food Frequency Questionnaire will be summarized for the FAS and PP Analysis Set, for each product use group at V1, as continuous variables as described in section 9.1.4.
- For the Lifestyle Questionnaire, scores for the 5 risk categories being collected in this study and the total score will be summarized for the FAS and PP Analysis Set, for each product use group at V1, as continuous variables as described in section 9.1.4.
- Selected endpoints (HDL-C, WBC, sICAM-1, 11-DTXB2, 8-epi-PGF2α, COHb (%), %pred FEV1 (post BD), and Total NNAL) defined as the "Smokers' Health Profile", will be further analyzed as described in section 9.6.2 for secondary endpoints. At the notable exception that all summaries will be stratified by region as well as the propensity score model to derive the ATT weight, while the analysis models will include the additional interaction term between group and region to derive region specific contrast for the comparison of interest.

9.6.5 Safety Evaluation

9.6.5.1 Adverse Events

AEs (including SAEs) will be collected from the time of ICF signature until the EOS for all enrolled subjects. Information recorded will include: verbatim description of the AE/SAE, start and stop dates, seriousness, severity (intensity), relatedness to study procedures, action taken

(e.g., whether or not the AE/SAE led to the subject's withdrawal from the study), and outcome (e.g., resolved, stabilized).

Adverse events (AEs) will be summarized for each product use group, including a total column, for the FAS. The number and percentages of subjects with at least one AE and the total number of AEs will be presented. Percentages will be calculated using the number of subjects in the corresponding product use group in the FAS as the denominator.

A summary showing the overall number of AEs, SAEs, severity, expectedness, relatedness, AE leading to death, AE leading to action taken and treatment given for an AE will be presented

The number and percentage of subjects with AEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Summaries will also be presented for AEs by relatedness to study procedures and AEs by severity. Tabulations will include both the number of subjects experiencing an event and the number of events.

Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

9.6.5.1.1 Serious Adverse Events (Including Deaths)

The number and percentages of SAEs will be summarized overall and by SOC and PT for each product use group. Tabulations will include both the number of subjects experiencing an event and the number of events.

Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

The number and percentage of deaths will be presented if applicable and AEs leading to death will be listed.

9.6.5.1.2 Adverse Events Leading to Discontinuation

If there are any AEs leading to discontinuation from the study, they will be summarized overall and by SOC and PT for each product use group.

9.6.5.2 Device Events

Not applicable.

9.6.6 Additional Assessments

9.6.6.1 Medical History and Concomitant Disease

Medical history (any condition that started and ended prior to Screening) and concomitant diseases (any condition ongoing at Screening) will be coded using MedDRA and listed separately.

Medical history and concomitant diseases will be summarized by product use group, system organ class (SOC) and preferred term (PT) for the FAS. The number and percentages of subjects with any medical history/concomitant disease will be presented along with the number and percentage of subjects who record each medical history/concomitant disease by SOC and PT. Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

9.6.6.2 Prior and Concomitant Medication

All medications will be listed by product using PT and Anatomical Therapeutic and Chemical (ATC) codes (WHODrug Global). A flag will be included in the listing to indicate whether the medication is prior or concomitant. See section 5.4 for derivation details.

Concomitant medications will be summarized by product use group for the FAS. The number and percentages of subjects who used the medication at least once will be presented by ATC 1st and 2nd levels and preferred drug name.

9.6.6.3 Physical Examination

Physical examination data will be listed. The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant results will be tabulated by body system according to Section 9.1.3.

9.6.6.4 Vital Signs

Heart rate (bpm), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) and respiratory rate will be summarized for each arm and overall, according to Section 9.1.3.

9.6.6.5 Spirometry

The Spirometry data is analyzed as part of Secondary Endpoint 1. See section 9.6.2 for details.

9.6.6.6 Electrocardiogram

Summary statistics for heart rate (bmp), PR interval (msec), QRS interval (msec), QT interval (msec), and corrected QT interval (msec) will be presented for each arm and overall, according to Section 9.1.3.

Each of ECG parameters mentioned above are classified as being normal, abnormal – clinically relevant, abnormal n not clinically relevant. The numbers and percentages for these categories, including the combined total abnormal classifications, will be presented according to Section 9.1.3 for each group and overall.

9.6.6.7 Assessment of Cough

The assessment of cough is analyzed as part of Secondary Endpoint 1. See section 9.6.2 for details.

10 ANALYSES AND REPORTING

10.1 Interim Analyses and Data Monitoring

Not applicable.

10.2 Safety Reporting

Not applicable.

10.3 Final Analyses

Final analyses for this study will be performed after database lock. A pre-analysis data review meeting, with data blinded where necessary (see Section 4.3.2), will be held prior to database lock.

Any post-hoc, additional exploratory analyses which were not identified in the SAP will be documented and reported as applicable. Any results from these unplanned analyses will be clearly identified in the CSR.

The list of tables, figures and listings to be presented are included in Section 13.4.

10.4 ClinicalTrials.Gov Reporting

Statistical summaries to be evaluated for publishing on the clinical trials.gov website will be flagged in the Section 13.4.

10.5 CSR In-Text Tables

It is planned that a subset of the final outputs will be adapted for use as in-text tables in the CSR. For improved efficiency, these outputs will be programmed at the same time as the final analyses. These outputs will be identified in Section 13.40.

11 DATA PRESENTATION

Unless specified otherwise in this document (see Section 9.1.4), data presentation will be consistent with the PMI style guide. Further details on data presentation can found in the output shells document in attachment 1.

12 REFERENCES

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13 APPENDICES

13.1 Study Assessments

Table A1: Study Assessments

	Visit 1	Safety Follow-up
Study Day	**Day 1**	**Day 2**
Prior to Enrollment		
Informed consent [a]	●	
Information on the risks of smoking and smoking/THS cessation advice	●	
Demographics [b]	●	
Medical history/concomitant diseases	●	
Prior/concomitant medication	●	
Questions on tobacco/nicotine-containing products use history	●	
Body height, weight and BMI	●	
CO breath test	●	
Alcohol breath test	●	
U: Drug screen [c]	●	
U: Cotinine test (cut-off ≥ 200 ng/mL or < 100ng/mL) [c]	●	
U: Pregnancy test (only female subjects) [c]	●	
U: Creatinine and BoExp to HPHCs/nicotine [c d]	●	
U: BoPH [d]	●	
U: Biobanking (if optional ICF signed) [d]	●	

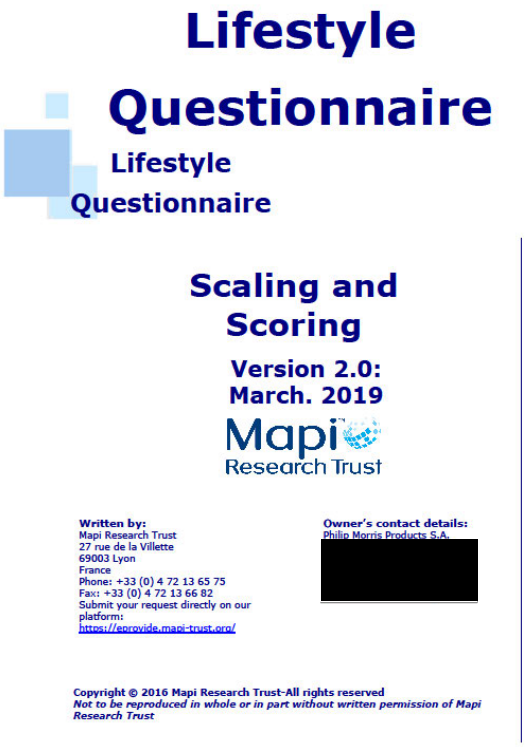
	Visit 1	Safety Follow-up
Study Day	**Day 1**	**Day 2**
Vital signs	●	
Physical examination	●	
ECG	●	
Spirometry pre- and post-bronchodilator	●	
Inclusion/exclusion criteria	●	
Enrollment	●	
After Enrollment		
Waist and hips circumference	●	
B: BoPH, BoExp and HbA1c	●	
Lifestyle Questionnaire	●	
Qualitative food group frequency questionnaire	●	
Questions on socioeconomic indicators	●	
ABOUT–Perceived risk	●	
ABOUT–Dependence	●	
SF-36	●	
Cough assessment	●	
Augmentation index and PWV	●	
FMD (only in selected centers)	●	
B: Biobanking (if optional ICF signed)	●	
AE/SAE recording	●	●
Discharge	●	

a. The informed consent process can be started as soon as the subject is invited to participate in the study, but the ICF must be signed before the first assessment at V1.
b. Sex, age and race.
c. The same spot urine collection will be used for pregnancy (all females), drug screen and cotinine tests, creatinine and for BoExp to HPHCs/nicotine. Sampling for BoExp should be performed as soon as possible, and samples frozen immediately. If enough urine could be collected, the same spot urine will be used for BoPH and Biobanking (if

additional optional ICF was signed). Otherwise another spot urine collection will be performed later during the visit. Urine samples should be processed according to laboratory manual/SHM.

d. These tubes will be discarded at the end of the visit if the subject is not enrolled.

13.2 Lifestyle Questionnaire Scoring Manual V2.0



13.3 Socio-Economic Indicators Harmonization

Countries	**Response options:** **educational categories (country specific) in English** Source for European countries: https://www.europeansocialsurvey.org/data/themes.html?t=sociodemo	**Harmonized educational level categories** Source for European countries: https://www.europeansocialsurvey.org/docs/methodology/education_upgrade_ESS1-4_e01_3.pdf EDULVLA Harmonized variable 1 - Less than lower secondary education EDULVLA Harmonized variable 2 - Lower secondary education completed EDULVLA Harmonized variable 3 - Upper secondary education completed EDULVLA Harmonized variable 4 - Post-secondary non-tertiary education completed EDULVLA Harmonized variable 5 - Tertiary education completed
English for the US	N/A (English equivalents of country specific educational categories are listed below)	Instruction for harmonization for harmonization across all countries and regions (30 Sept 2020) No translation needed.
Czech for Czech Republic	0. Uncompleted primary 1 Primary 2. Vocational, no upper diploma 3. Secondary, no upper diploma 4. Vocational, diploma 5. Secondary technical, diploma 6. Secondary academic, diploma 7. Higher 8. Tertiary, Bc. 9. Tertiary, M.A. 10. Post-graduate 11. Prefer not to say	EDULVLA Coding frame: ("country specific source variable" to "harmonized") source variable "0"converted to harmonized variable"1", source variable "1"converted to harmonized variable to "2", source variable "3-6" converted to harmonized varibale "3", source variable "7-10" converted to harmonized varibale "5".

German for Germany	0.left school without school leaving qualification 1. Primary education 2. Basic education 3. Higher education entrance qualification, but not for university 4. Higher education, entrance for university 5. Vocational education/ apprenticeship 6. Higher vocational specialization 7. Tertiary education – Bachelor 8. Tertiary education – Master 9. Tertiary Education – PhD 10. Prefer not to say	• Source variable “0”, “1”, “2” converted into harmonized variable “1”, • Source variable “3” converted to harm. var.“2”, • Source variable “4” converted to harm. var. “3”, • Source var. “5” converted to harm. var. “4”, • Source var. “6-9” converted to harm. var. “5”
Greek for Greece	0. Analphabetic (not knowing reading and writing),not completed primary education/only feof primary education,1. Primary education, 2. Lower secondary education (i.e. only few classes of secondary education, night school, technical vocational schools) 3. Upper secondary education,4. Post-compulsory Secondary education/non-tertieary education (i.e. Publuc and Private Vocational Traning Institutes etc.)5. Higer Education: University Diplomas holders and Technical Educational Institutes Diplomas holders,6. MA Degree,7. PhD Degree8. Prefer not to say	source variables "0 and 1" converted to harmonized "1"source variable "3" remains harmonized "3", source variables "4-7" converted to harmonized "5"
Italian for Italy	0. Not completed primary education, 1. primary of first stage of basic, 2. Lower secondary or second stage of basic, 3. upper secondary, 4. Post secondary, non-tertiary, 5. First stage of tertiary, 6. Second stage of tertiary 7. Prefer not to say	source variable "0 and 1" converted to harmonized"1" , source variable "2" remains "2", source variable "3" remains "3", source variable "4-6" converted to harmonized "5"

Portugese for Portugal	1. None, 2. Basic Level 1(primary school - 4th year), 3. Basic level 2 (preparatory school, 5th and 6th years), 4 Basic level 3 (9th year/ previous 5th year of high school), 5 Secondary Education - Vocational Training, 6 Secondary School (12th year/ previous 7th year of high school) 7. Training in Technological Specialization, 8. Tertiary Education - Bachelor, 9. Tertiary Education - Degree 10. Tertiary Education - Master (Before Bologna) 11. Tertiary Education - Master (After Bologna) 12. Tertiary Education - PhD 13. Prefer not to say	source variable "1-3" converted to harmonized "1", source variable "4" converted to harmonized "2", sourve variable "5-6" converted to harmonized "3", source variable "7" converted to harmonized "4", source varable "8-12" converted to harmonized "5".
Romanian for Romania	1. No school, 2. Primary school, 3. General school (or lower secondary), 4. Vocational and apprenticeship school, 5. High school (Upper secondary), 6. Post-high school and 2 or 3 years colleges, 7. University degree (4 or 5 years colleges), 8. Post-graduate degree, 9. Prefer not to say	source variable "1 and 2" converted to harmonized "1", source variable "3" converted to harmonized "2", source variable "4 and 5" converted to harmonized "3", source variable "6" converted to harmonized "4", source variable "7 and 8" converted to harmonized "5",
Russian for Russia	1. Primary education,2. Incomplete high school,3. Professional education without secondary education,4. Completed secondary level,5. Professional education on secondary level,6. Special technical education,7. Several grades of college with no certificate, 8. Bachelor degree from college,9. Master degree from college,10. Completed college by 5-6 grade system,11. Post-colllege education without scientific degree,12. Scientific degree,13. Prefer not to say§	source variable " 1" converted to harmonized "1", source variable "2-3" converted to harmonized "2", source variable "4, 5 and 7" converted to harmonized "3",source variable "6, 8, 9, 10, 11, 12" converted to harmonized "5",

Ukrainian for Ukraine	0. Not completed primary (compulsory) education (less than 4 years of secondary school) 1. Primary education (4-7 years of secondary school) 2. Uncompleted secondary education (certificate of 8-9 years of secondary school) 3. Professional-Technical School on the base of uncompleted secondary education 4. Completed secondary education (certificate of 10-11 years of secondary school), 5. Professional-Technical School on the base of completed secondary education 6. Additional education on the base of completed secondary education (professional courses, comprehensive courses etc.) 7. Uncompleted high education (diploma of college) 8. Basic high education (bachelor degree) 9. Completed high education (specialist degree, master degree) 10. Postgraduate studies, scientific degree, 11. Prefer not to say	source variable "0 and 1" converted to harmonized "1", source variable "2 and 3" converted to harmonized "2", source varaible "4" converted to harmonized "3", source variable "5 and 6" converted to harmonized "4", source variable "7, 8, 9, 10" converted to harmonized "5",
Russian for Ukraine	0. Not completed primary (compulsory) education (less than 4 years of secondary school) 1. Primary education (4-7 years of secondary school) 2. Uncompleted secondary education (certificate of 8-9 years of secondary school) 3. Professional-Technical School on the base of uncompleted secondary education 4. Completed secondary education (certificate of 10-11 years of secondary school), 5. Professional-Technical School on the base of completed secondary education 6. Additional education on the base of completed secondary education (professional courses, comprehensive courses etc.) 7. Uncompleted high education (diploma of college) 8. Basic high education (bachelor degree) 9. Completed high education (specialist degree, master degree) 10. Postgraduate studies, scientific degree, 11. Prefer not to say	source variable "0 and 1" converted to harmonized "1", source variable "2 and 3" converted to harmonized "2", source varaible "4" converted to harmonized "3", source variable "5 and 6" converted to harmonized "4", source variable "7, 8, 9, 10" converted to harmonized "5",

Japanese for Japan	0 (No formal qualification), 1 (lowest formal qualification), = elementary school2 (Above lowest qualification), = junior high school3 (Higher secondary completed), = senior high school4 (Above higher secondary level) = college/technical college5 (University degree completed) = university/ Postgraduate6 Prefer not to say	Source variable 0,1 = EDULVLA Harmonized variable 1 Source variable 2 = EDULVLA Harmonized variable 2 Source variable 3 = EDULVLA Harmonized variable 3 Source variable 4 = EDULVLA Harmonized variable 4 Source variable 5 - EDULVLA Harmonized variable 5
Korean for South Korea	0 (No formal qualification), 1 (lowest formal qualification), = primary school 2 (Above lowest qualification), = lower secondary school 3 (Higher secondary completed), = senior secondary school/vocational school 4 (Above higher secondary level) = Junior college (associate degree, Bsc) 5 (University degree completed) = University or postgraduate (MSc, doctoral degree) 6 Prefer not to say	Source variable 0,1 = EDULVLA Harmonized variable 1 Source variable 2 = EDULVLA Harmonized variable 2 Source variable 3 = EDULVLA Harmonized variable 3 Source variable 4 = EDULVLA Harmonized variable 4 Source variable 5 = EDULVLA Harmonized variable 5

13.4 Tables, Figures & Listings

The list of tables, figures and listings is currently in a separate excel file.