PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

ZRHR-ERS-09-EXT-US

Study Title:	A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study.
Short Title:	A 26 week extension of the ZRHR-ERS-09-US study evaluating biological and functional changes in healthy smokers after switching to THS 2.2.
Registration Number:	Not assigned
Study Number	ZRHR-ERS-09-EXT-US
Product Name:	Tobacco Heating System 2.2 (THS 2.2)
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version Number:	Final Version 3.0
Revision Date:	23 August 2016
Authors:	[redacted], Clinical Scientist [redacted], PhD, Study Statistician [redacted], MD, Medical Safety Officer

SYNOPSIS

Sponsor:

Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Product Name:

Tobacco Heating System 2.2 (THS 2.2)

Study Title:

A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study.

Study Number:

ZRHR-ERS-09-EXT-US

Short Study Title:

A 26 week extension of the ZRHR-ERS-09-US study evaluating biological and functional changes in healthy smokers after switching to THS 2.2.

Primary Objective and Endpoints:

The primary objective of this study is:

1. To determine the changes to the selected clinical risk endpoints ("smokers' health profile") in smokers who have switched from CC to THS 2.2 as compared to those who continued to smoke CC during the extension study.

   Endpoints included in the "smokers' health profile" measured at V16 (Week 52):

   - High density lipoprotein cholesterol (HDL-C) in serum.
   - White blood cell total count (WBC) in blood.
   - Soluble intercellular adhesion molecule 1 (sICAM-1) in serum.
   - 11-dehydrothromboxane B2 (11-DTX-B_2) in urine (expressed as concentration adjusted for creatinine).
   - 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) in urine (expressed as concentration adjusted for creatinine).

- Carboxyhemoglobin (COHb) in blood.
- Forced expiratory volume in 1 second (FEV_1 post-bronchodilator, expressed as % predicted [FEV_1 %pred]).
- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) in urine (expressed as concentration adjusted for creatinine).

Secondary Objectives and Endpoints:

The secondary objectives of this study are:

2. To evaluate self-reported product use (CC and THS 2.2) over the duration of the study.

   Endpoint (measured daily):

   - Number of CC or THS Tobacco Sticks used daily as reported in the self-reported product use electronic diary.

3. To determine the reduction in exposure to harmful and potentially harmful constituents (HPHCs) in smokers who have switched from CC to THS 2.2 as compared to those who continued to smoke CC.

   Endpoints at V16 (Week 52):

   - Biomarker of exposure (BoExp) to carbon monoxide (CO): CO in exhaled breath (expressed as ppm).
   - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN) in urine (expressed as concentration adjusted for creatinine).

4. To determine the levels of nicotine exposure in smokers who have switched from CC to THS 2.2 as compared to those who have continued to smoke CC.

   Endpoints (BoExp to nicotine) over the duration of the study:

   - Nicotine equivalent (Neq): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide in urine (expressed as concentration adjusted for creatinine).
   - Nicotine and cotinine in plasma expressed in ng/mL.

5. To describe the changes of biological or functional markers associated with respiratory diseases and cardiovascular diseases (CVD) in smokers who have switched from CC to THS 2.2 as compared to those who have continued to smoke CC.

   Endpoints associated with respiratory diseases measured at V16 (Week 52):

   - Lung function:

- Spirometry pre- and post-bronchodilator: FEV_1, forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow (FEF 25-75) and bronchodilator reversibility in FEV_1.
- Lung volume pre-bronchodilator: forced residual capacity (FRC), vital capacity (VC), total lung capacity (TLC), and inspiratory capacity (IC).
- Cough symptoms (intensity and frequency), amount of sputum production, and bothersomeness of cough symptom from the cough questionnaire.

Endpoints associated with CVD measured at V16 (Week 52):

- Myeloperoxidase (MPO), apolipoprotein A1 and B (Apo A1 and Apo B), high sensitivity C-reactive protein (hsCRP), and low density lipoprotein cholesterol (LDL-C), in serum.
- Fibrinogen and homocysteine in plasma.
- Albumin in urine (expressed as concentration adjusted to creatinine).
- Platelet count and hemoglobin glycosylated (HbA1c in whole blood).
- Blood pressure, weight, and waist circumference.

6. To describe the changes in subjective effects of smoking in smokers who have switched from CC to THS 2.2 as compared to those who have continued to smoke CC.

   Endpoint over the duration of the study:

   - Product evaluation: subscales from the modified cigarette evaluation questionnaire (MCEQ).

7. To describe the intention to use THS 2.2 in smokers who have switched from CC to THS 2.2.

   Endpoint at V16 (Week 52):

   - Intention to use associated with THS 2.2: item scores from intent to use questionnaire for THS 2.2 (ITUQ) only for subjects in the THS 2.2 arm.

8. To describe the change in tobacco dependence in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoints at V16 (Week 52):

   - Score from the Fagerström (FTND) questionnaire.
   - Time to first cigarette from the FTND questionnaire.

9. To describe the effect of combined product use (dual use) over the study on the components of the "smokers' health profile".

   Endpoint:

   - The levels of the components in the "smokers' health profile" and the number of CC and THS Tobacco Sticks used daily as reported on the self-reported product use electronic diary.

10. To evaluate the safety profiles associated with THS 2.2 and CC.

    Endpoints over the duration of the study:

    - Adverse events (AEs), serious adverse events (SAEs) and device events, including THS 2.2 malfunction/misuse.
    - Vital signs.
    - Electrocardiogram (ECG).
    - Clinical chemistry, hematology and urine analysis safety panel.
    - Physical examination.
    - Concomitant medications.

Study Hypothesis:

No hypotheses are to be tested. The objective of the study is to determine the effect of THS 2.2 compared to CC at week 52 on the components of the "smokers' health profile" as defined by PMI (Table S1), and to provide additional information to the results of the original study (ZRHR-ERS-09-US) for a prolonged exposure period.

Table S1 The "Smokers' Health Profile"

Biomarker	Measurement of	Biofluid/Function
Cardiovascular Disease		
High density lipoprotein cholesterol	Lipid metabolism	Serum
Soluble intercellular adhesion molecule 1	Endothelial dysfunction	Serum
White blood cell count	Inflammation	Blood
Carboxyhemoglobin	Transport of oxygen by hemoglobin	Blood
11-Dehydrothromboxane B_2	Platelet activation	Urine
8-epi-prostaglandin $F_{2\alpha}$	Oxidative stress	Urine
Respiratory Disease		

Forced expiratory volume in 1 second	Lung function	Lung function
Genotoxicity		
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	Exposure to carcinogenic HPHC (NNK)	Urine

Evaluation criterion:

The study will target to describe the 95% confidence intervals (CI) of the THS 2.2 effect as compared to CC at week 52 on the components of the "smokers' health profile" estimated with a precision of ±75% of the anticipated THS 2.2 effect at week 52.

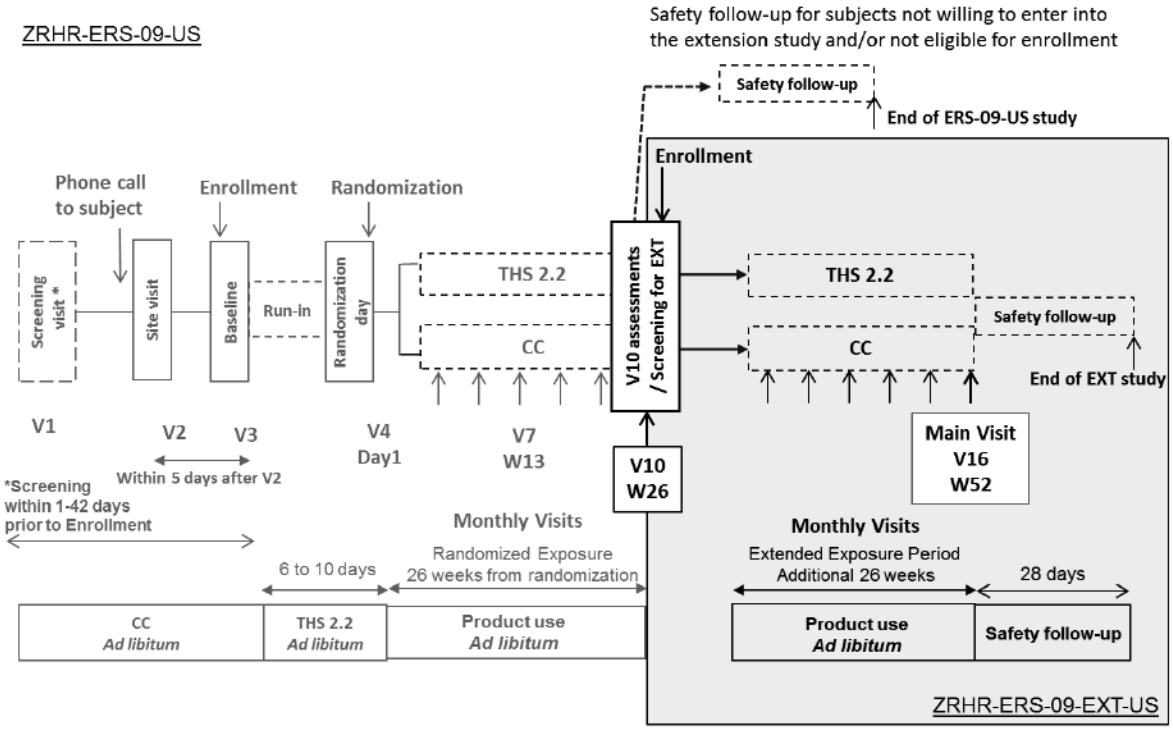
Study Design:

This study is a 26 week extension study of the original study (ZRHR-ERS-09-US), a randomized, controlled, open-label, 2-arm, parallel group study design conducted over a 26 week period. This extension study will be conducted as a separate study, as a follow-up of the randomized exposure period of the original study, extending the exposure from V10 (Week 26) to V16 (Week 52), but will be using the same sites. Subjects will continue to use the product they were randomized to in the original study (THS 2.2 arm or CC arm).

The extension study will be an *ad libitum* smoking study with unrestricted product use for the duration of the study (including during site visits).

End of Study for whole study is the last subject individual EOS.

Subjects that terminate the study after enrollment and prior to completion of the extension study will undertake early termination procedures (section 9.4).



Abbreviations: CC = conventional cigarette(s); THS = Tobacco Heating System

Figure 1 Study Design

The V10 (Week 26): screening and enrollment into the extension

V10 represents both the last visit of the main study as well as the first of the extension study. For subjects willing to participate in the extension study, it also corresponds to the first visit in the extension study. Once all V10 assessments from the original study have been performed, subjects will be offered to enter into the extension study. The enrollment can only take place at V10.

Enrolled subjects will be informed to continue to use the product they were randomized to in the original study as follows:

- THS 2.2 arm: use of THS 2.2 *ad libitum*.
- CC arm: use of their own CC brand *ad libitum*.

Subjects who do not sign the ICF for the extension study, will enter the 28 day safety follow-up period of the original study.

Subjects who sign the ICF for the extension study but do not meet the entry criteria will be considered as screening failure and will enter the 28 day safety follow-up period of the

original study. If the subject withdraws or is removed from the study after enrollment, he/she will enter the safety follow up period of the extension study (section 9.3).

The Extended Exposure Period (from Check-out of V10 [Week 26] until Check-out of V16 [Week 52]):

Enrolled subjects will continue to use the product they were randomized to in the original study (THS 2.2 arm or CC arm) in an ambulatory setting for an additional 26 weeks *ad libitum*, including during the visits. Subjects will continue to capture the number of each of the products used including THS Tobacco Sticks, CC (menthol and non-menthol), and other nicotine/tobacco containing products on a daily basis in a product use diary.

After V10, subjects will be required to come for 6 monthly visits to the site for resupply of THS 2.2 (except for V16) and for safety assessments. The visits will be scheduled with a time window of +/- 5 days respective to V4 of the original study:

- V11 (30 weeks after V4, 210 days +/- 5 days),
- V12 (35 weeks after V4, 245 days +/- 5 days),
- V13 (39 weeks after V4, 273 days +/- 5 days),
- V14 (43 weeks after V4, 301 days +/- 5 days),
- V15 (48 weeks after V4, 336 days +/- 5 days),
- V16 (52 weeks after V4, 364 days +/- 5 days).

At V15, containers to collect 24 hour urine will be distributed to the subjects. Twenty four-hour urine collection will start in the morning of the day before V16 and will end 24 hours later on the morning of V16. At V16, blood and urine samples from the 24 hour urine collection will be collected by the site for the assessments of BoExp and clinical risk endpoints.

Any subject, who wants to make a quit attempt from using tobacco-containing products (e.g. THS 2.2 and CC) during the study, will be encouraged to do so and will be referred to appropriate services. The subject will not be discontinued from the study, will come to all scheduled visits for assessments, and his/her financial compensation will not be affected. A subjects in the THS 2.2 arm, who decides to quit using tobacco-containing products (THS 2.2 and CC), will return all the THS 2.2 components given during the study and will not be provided with THS 2.2 anymore, starting from the day the participant intends to quit onwards.

The Safety Follow-up Period (from the Check-out of V16 (Week 52) plus 28 days):

At the end of the extended exposure period (i.e., or study completion on V16), subjects will enter into a safety follow-up period for 28 days. During the safety follow-up period, spontaneously reported and ongoing AE/SAEs will be actively monitored by the site. The

end of study (individual) is defined as the check-out of the subject on V16 or the date of early termination of the subject plus a 28 day safety follow-up period, if applicable. For further information on safety follow-up requirements refer to section 9.3.

Study Population and Main Criteria for Inclusion/Exclusion:

All subjects who have completed the 26 week randomized exposure period (V10) of the original study will be potentially eligible for enrollment into the extension study, depending on whether or not they want to participate and if they meet the entry criteria.

The maximum number of subjects that can be enrolled is pre-defined by the number of subjects completing the 26 week period of the original study. Entry criteria for enrollment into the extension study are listed below.

Inclusion criteria:

- Subject completed V10 of the original study (ZRHR-ERS-09-US).
- The subject is willing to comply to study procedures and to continue to use the product he/she was allocated to during the original study (THS 2.2 or CC) for an additional 26 weeks at V10.
- Subject has given written informed consent to enter the 26 week extension study at V10.

Exclusion Criteria:

- As per judgment of the PI(s) or designee(s), the subject cannot participate in the study for any reason (e.g. medical, psychiatric and/or social reason).
- Any medical conditions that in the opinion of the PI(s) or designee(s) would jeopardize the safety of the participant.
- Subject has made a quit attempt from using tobacco-containing products (e.g. CC and THS 2.2) during the original study.
- Pregnant or breast feeding female at V10.
- Female who does not agree to use an acceptable method of effective contraception.

Investigational Products:

Test Product:

Tobacco Heating System 2.2 (THS 2.2) which has three major parts: the THS Tobacco Stick, the THS Tobacco Stick Holder (Holder), and the Charger.

Reference Product:

Subject's own supply of commercially available own brand CC (manufactured and hand-rolled). CC will not be provided by the Sponsor.

Duration of Study:

The entire extension study duration per subject will be up to 26 weeks of exposure (6 months) plus 28 days of safety follow-up.

Statistical Methods:

The analysis of the "Smokers' Health Profile" at V16 will compare the two study arms according to subjects' exposure (THS 2.2 or CC) with respect to:

- Mean difference in each of the following endpoints: FEV_1 %pred, HDL-C, and WBC at V16.
- Ratio of the geometric mean levels of each of the following endpoints: 11-DTX-B2, sICAM-1, 8-epi-$PGF_{2\alpha}$, COHb, and total NNAL at V16.

The endpoints will be analyzed using a generalized regression model adjusting for site, sex, Baseline value of the endpoint and other endpoint specific covariates. The baseline values originate from the original study.

Descriptive statistics for continuous variables (number of subjects [n], number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation [SD], median, first and third quartiles, minimum and maximum for continuous data, including geometric mean and coefficient of variation for data analyzed in the log scale; frequency counts and percentages for categorical data) will be presented at each time point, where applicable.

Analyses over time will be descriptive statistics of parameters at each assessment time point, together with mean difference from Baseline and 95% confidence intervals (CI).

Safety will be summarized for the safety population according to study arm and according to product exposure.

Sample Size:

The sample size for this study was defined based on the sample size requirements of the original study, for which the sample size was calculated to ensure an overall study power of at least 90% while maintaining at least 80% power to detect the expected effect of THS 2.2 as compared to CC for each individual endpoint of the "Smokers' health profile", over 26 weeks of exposure. This required 475 subjects randomized per group accounting for an anticipated 75% of the THS 2.2 arm to be Mostly THS 2.2 users (i.e. report at least 70% THS 2.2 use).

Based on the assumptions that 30% of the 950 subjects will not be enrolled or will drop out from the extension study and a potential decrease from 75% to 50% of Mostly THS 2.2 users among subjects randomized to THS 2.2, the study will have at least 90% probability to determine the effect of THS 2.2 as compared to CC on FEV_1 at V16 with a margin of error (95% CI) of at most ±1.5 %pred. The anticipated SD of 6.4 %pred was estimated using the results of the "Lung Health Study" [1].

Following our current understanding of product use data in the main study, the definition of the product use categories was redefined and the underlying assumptions re-evaluated so that approximately 60% of the subjects in the THS 2.2 arm are expected to be in the THS-use category, with an anticipated 20% of subjects dropping out or reporting insufficient product use data in the two arms of the main study. Based on the 65% rate of enrollment into the extension study observed among subjects randomized in the main study, the extension study will have more than 90% probability to determine the effect of THS-use compared to CC-use on FEV1 at V16 with a margin of error (95% CI) of at most ±1.5 %pred.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

11-DTX-B_2	11-dehydro-thromboxane B2
8-epi-$PGF_{2\alpha}$	8-epi-prostaglandine F2 α
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
B	Blood sample required
BMI	Body mass index
BoExp	Biomarker(s) of exposure
BP	Blood pressure
BUN	Blood urea nitrogen
CC	Conventional cigarette
CD	Compact disc
CEMA	2-cyanoethylmercapturic acid
CFR	Code of Federal Regulations
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CTMS	Clinical trial management system
CV (statistics)	Coefficient of variation

CVD	Cardiovascular disease
DMP	Data management plan
ECG	Electrocardiogram
CRF	Case report form
ePRO	Electronic patient reported outcome
EOS	End of study
ERS	Exposure Response Study
FAS-EX	Full analysis set – as exposed
FAS-AR	Full analysis set – as randomized
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GVP	Gas vapor phase
HbA1c	Hemoglobin glycosylated A1c
HDL-C	High density lipoprotein-C
HIPAA	Health Insurance Portability and Accountability Act
HPHCs	Harmful and potentially harmful constituents
hsCRP	High sensitive C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IC	Inspiratory capacity
IOM	Institute of Medicine
IP	Investigational product
IRB	Institutional Review Board

ISO	International Organization for Standardization
ITUQ	Intent-to-use questionnaire
IV	Intravenous
IXRS	Interactive voice and web response system
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein-cholesterol
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MCEQ	Modified cigarette evaluation questionnaire
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
MRTP	Modified risk tobacco product
MPO	Myeloperoxidase
n	Number of subjects
Neq	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NSAID	Non-steroidal anti-inflammatory drug
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMI	Philip Morris International
PP	Per-protocol
PT	Preferred term
QC	Quality control
RBC	Red blood cell (count)

SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SES	Socio-economic status (questionnaire)
sICAM-1	Soluble intercellular adhesion molecule-1
SMP	Safety management plan
SOC	System organ class
SOP	Standard operating procedure
TC	Total cholesterol
TG	Triglycerides
THS 2.2	Tobacco Heating System 2.2
THSts	THS Tobacco Stick
TLC	Total lung capacity
TPM	Total particulate matter
U	Urine sample required
[redacted]	[redacted]
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
USB	Universal serial bus
VAS	Visual analog scale
VC	Vital capacity
WBC	White blood cell (count)
WHO	World Health Organization

Explanation of Terms

The following special terms are used in this protocol:

Original study	Refers to the original study: ZHRH-ERS-09-US
Extension study	Refers to the extension study: ZHRH-ERS-09-EXT-US
End of study (individual)	Date of the last visit of the subject plus 28 days of Safety Follow-up Period. For subjects lost to follow-up the individual end of study is the discontinuation date.
End of study (whole study)	End of Study for whole study is the last subject individual EOS.
Conventional cigarette (CC)	The term "conventional cigarette" refers to commercially available cigarettes (manufactured and hand-rolled) and excludes cigars, pipes, bidis, and other nicotine-containing products.
Screening failure	Subjects who signed the informed consent form (ICF) at V10 but do not meet the entry criteria will be considered as screening failure. Once excluded, subject will not be allowed to re-enter the study.
Tobacco Heating System 2.2 (THS 2.2)	THS 2.2 comprises the following components: a THS Tobacco Stick, the THS Tobacco Stick Holder (Holder), a Charger, a Cleaning Tool, a main power supply, and a USB cable.

1 ETHICS AND REGULATIONS

1.1 Institutional Review Board Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] including the subject information sheet, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's brochure [IB], available safety information, curriculum vitae of the Principal Investigator(s) (PI(s)) and designee(s) and/or other evidence of qualifications and any other documents requested by an Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB according to the appropriate provisions found in 21 Code of Federal Regulations (CFR) part 50 ("Informed Consent of Human Subjects") and 21 CFR part 56 ("Institutional Review Boards"). The IRB shall be appropriately constituted and perform its functions in accordance with the International Conference on Harmonization (ICH) Tripartite Guidance for Good Clinical Practice (GCP) [2] and local requirements, as applicable.

In accordance with GCP and 21 CFR part 56, a written confirmation of the IRB approval should be provided to the Sponsor. This should identify the study (name of the PI(s) and designee(s), study number, and title) and the documents that have been approved by the IRB, with dates and version numbers, as well as the date of approval. The composition of the IRB, including the name and occupation of the chairperson, will be supplied to the Sponsor together with a GCP compliance statement.

The written approval from the IRB will be filed in the Principal Investigator file, and a copy will be filed in the study master file at the Sponsor or designated organization. The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB.

Any substantial change or addition to this protocol will require a written protocol amendment that must be approved by the Sponsor and the Principal Investigator(s). All amendments will be submitted to the IRB, and substantial amendments will only be implemented after approval by the IRB.

These requirements for approval should in no way prevent any action from being taken by the PI(s) or designee(s) or by the Sponsor in order to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the PI(s) or designee(s), and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately. The PI(s) is (are) responsible for local reporting (*e.g.*, to the IRB) of serious adverse events (SAEs) that occur during the study, according to local regulations.

Relevant safety information will be submitted to the IRB during the course of the original and the extension studies in accordance with national regulations and requirements. Medically qualified study personnel will be available during the study.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [3] and are consistent with ICH/GCP [2] applicable regulatory principles.

The PI(s) or designee(s) agree(s) to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IRB. The PI(s) and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki is located in the Investigator's study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

During V10 of the extension study, the PI(s) or designee(s) will ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the extension study, and the PI(s) or the designee(s) will answer all questions the subject might have to his/her full satisfaction. The subject will have sufficient time for consideration of his/her participation in the study and will be notified that he/she is free to withdraw from the study at any time.

Once the subject has received all the necessary information, and if he/she agrees to participate in the study, the subject and the person who conducted the inform consent discussion during V10 will both sign, date and time the ICF. The ICF includes both the subject information sheet and informed consent. No study-specific procedures will be performed before the ICF has been signed (including date and time).

The original, dated and signed ICF(s) must be kept by the PI(s) and filed in the Principal Investigator's file at the site or with the subject's files and a copy must be given to the subject.

The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless he/she disagrees. The subject will be informed that additional data analysis not mentioned in the protocol or in the statistical analysis plan (SAP) might be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Informed Consent Form for Long-term Biobanking

In addition to the ICF for the participation in the extension study, only subjects who have previously provided consent for biobanking (and did not withdraw it) will be asked to provide his/her separate optional consent at V10 for the collection of samples and storage for long-term biobanking, which will be performed at V16:

- One separate ICF to obtain consent for serum, plasma and urine collection, and long-term storage for subsequent analysis of biomarkers of exposure (BoExp) and clinical risk endpoints following completion of this study.
- One separate ICF to obtain consent for collection and long-term storage of blood and plasma for further analysis of transcriptomics and lipidomics respectively.

Each subject will be given full and adequate oral and written information about the nature, purpose, possible risks and benefits of biobanking, and the PI(s) or designee(s) will answer all questions the subject might have until full satisfaction. The subject will be notified that he/she is free to withdraw his consent at any time. Once the subject has received all the necessary information, and if he/she agrees to participate, this will be documented by the date, time and signature of both, the subject and the PI(s) or designee(s) who conducted the informed consent discussion. The subject's consent to collection of any samples for long-term storage in a biobank is not a requirement for his/her participation to the study (section 1.3.1).

Collection of samples and storage for long-term biobanking performed at V10 is already part of the original study, and subjects should have signed the separate optional consent forms at V1.

1.3.3 Amendment to the Informed Consent Form

If a protocol amendment is required, or if any new information regarding the risk profile of the investigational product (IP) becomes available for any other reason deemed necessary, an amendment to the ICF may be required. If a revision of the ICF is necessary, the PI(s) or designee(s) will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IRB before subjects are required to re-sign the ICF (including date and time). If new and important safety information is received, subjects who already completed or are discontinued from the study will be informed by letters, emails or phone calls.

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, PI(s) or designee(s) abide by the principles of the ICH guidelines on GCP [2]. These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting clinical studies of tobacco products following the United States Food and Drug Administration (FDA) guidelines on modified risk tobacco product (MRTP) [4]. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [3].

In addition, the PI(s) or designee(s) will carry out the clinical study in accordance with applicable national and local laws of the pertinent regulatory authorities.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette smoking causes pulmonary, cardiovascular diseases and other serious diseases in smokers [5]. 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 do not manage to quit or decide to continue smoking. To those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases. These products are now referred by the FDA as modified risk tobacco products (MRTPs) [4].

Philip Morris International (PMI) develops candidate MRTPs with the objective to substantially reduce the exposure to harmful and potentially harmful constituents (HPHCs) while providing an acceptable option to smokers as substitutes for conventional cigarettes (CC). The approach to achieve this is by heating tobacco at lower temperatures rather than burning tobacco as it is the case for CC. In this way a large spectrum of HPHCs are eliminated or reduced, and the PMI clinical program aims to substantiate reduced risk for smoking-related diseases with the new heated tobacco products.

A dose-response relationship exists between cigarette smoking exposure and smoking-related diseases such as chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), and lung cancer. Several functional and biological markers (clinical risk endpoints) referring to smoking-related adverse health effects are favorably changed upon smoking cessation (SC) and are sufficiently sensitive to smoking status to be used for the risk assessment of our candidate MRTP, the Tobacco Heating System 2.2. (THS 2.2) As part of the global clinical program to assess the risk reduction using THS 2.2, a smoking cessation study of 1 year duration (SA-SCR-01) is being conducted in parallel to the ZRHR-ERS-09-US study and its extension study, 2-arm parallel randomized studies comparing smokers switching from CC to THS 2.2 and smokers continuing smoking CC for 26 weeks and 52 weeks, respectively. The observed changes in the clinical risk endpoints and biomarkers of exposure after switching from CC to THS 2.2 will be compared to smoking abstinence for a total of 52 weeks (26 weeks + 26 additional weeks) building the basis of the comparative risk assessment between THS 2.2 and CC.

2.1.2 Description of the Product and Scientific Findings

Thousands of chemicals - “smoke constituents” - are formed when tobacco is burned or combusted. More than 6000 smoke constituents have been identified [6], and more than 100 of them have been categorized as HPHCs [7].

The product developed by PMI, and to be assessed in this study, is the 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 CC, which can reach 900°C. THS 2.2 is composed of the THS Tobacco Stick Holder, dedicated special THS Tobacco Sticks made of tobacco, a Charger, and different accessories. The energy of the THS Tobacco Stick Holder is sufficient to maintain approximately a 6-minute session. Unlike CCs, the THS Tobacco Sticks do not burn down during their consumption and their lengths remain the same after use.

The non-clinical assessment of THS 2.2 described in the Investigator's brochure Edition 4 (November 2014) supports the conduct of the clinical study ZRHR-ERS-09-US and its extension study[8]. No new or increased toxicological hazard in the product's aerosol was detected compared with CC smoke.

Several clinical studies have been conducted on THS 1.0, an earlier development version of THS 2.2, in Europe, Asia, Africa and the United States. All studies showed reductions in exposure to the majority of measured HPHCs from both aerosol fractions, total particulate matter (TPM) and gas vapor phase (GVP), in subjects using the THS 1.0 as compared to subjects continuing smoking CC, both, in controlled and ambulatory setting. THS 2.1, the immediate predecessor of the non-menthol THS 2.2, was tested in two exploratory clinical studies to measure the nicotine pharmacokinetic profile (PK) [9] and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1 [10]. The observed nicotine PK profile for THS 2.1 was similar to CC and there were significant reductions in the exposure to the majority of selected HPHCs [11]. In 2013, four clinical studies were initiated in US, Europe, and Japan in order to evaluate the nicotine PK profile, to demonstrate reduced exposure, and to determine functional and biological changes following the switching from CC to non-menthol THS 2.2 in smokers as compared to smokers continuing smoking CC. These studies are currently in different phases of finalization and the results will be incorporated in the next edition of the Investigator Brochure.

Clinical studies conducted and ongoing so far on a few hundred of subjects revealed no safety concern for THS 2.2 and its earlier prototypes.

2.2 Purpose of the Study

The objective of the study is to determine the effect of THS 2.2 compared to CC at week 52 on the components of the "smokers' health profile" as defined by PMI, (Table 1) to provide additional information to the results of the original study (ZRHR-ERS-09-US) for a prolonged period of time.

Table 1 The "Smokers' Health Profile"

Biomarker	Measurement	Matrix/ Function	Timeframe of Reversibility upon Smoking Cessation
Cardiovascular Disease			
High density lipoprotein Cholesterol (reviewed in [12])	Lipid Metabolism	Serum	Within 3 months
Soluble intercellular adhesion molecule-1 [13-15]	Endothelial Dysfunction	Serum	Within 4 weeks
White blood cell count (total count) [16-19]	Inflammation	Blood	Within 6-12 months
Carboxyhemoglobin [20, 21]	Transport of oxygen by hemoglobin	Blood	Within 1-7 days
11-Dehydrothromboxane B_2 [22-24]	Platelet activation	Urine	Within 2-4 weeks
8-epi-prostaglandin [25, 26]	Oxidative stress	Urine	Within 1-2 weeks
Respiratory Disease			
Forced expiratory volume in 1 second [27-30]	Lung function	Lung function	Within 6-12 months
Genotoxicity			
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) [31, 32]	Exposure to carcinogenic HPHC (NNK)	Urine	Within 3 months

Additional clinical risk endpoints related to cardiovascular and respiratory diseases will be assessed in this study.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Advice on health risk associated with tobacco smoking and smoking cessation advice will be provided at each visit from V11 to V16. The advice will follow the recommendations of the U.S. Public Health Service [33, 34]. Subjects who are motivated to quit using tobacco-containing products (e.g. THS 2.2 and CC) are to be referred for additional smoking cessation counselling.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures.

- Risks related to blood sampling (*e.g.*, excessive bleeding, fainting, hematoma, paresthesia or infection).
- Risks related to drug application as part of testing procedures (*i.e.*, spirometry with short-acting bronchodilator).
- Risk related to spirometry testing procedures (e.g., dizziness or fainting).

2.3.3 Anticipated Foreseeable Risks due to the Investigational Products (THS 2.2/CC)

- Change in smoking habits due to study requirements and related concomitant symptoms, (*e.g.*, craving, withdrawal symptoms).
- All risks related to study procedures and IP will be explained in details to the subjects. Mitigation will include:
  - Using accepted research and scientific standards, (*e.g.*, blood samples not to exceed local blood donation standards).
  - Medical assessment, management of all study participants with follow-up of those who have experienced an AE/SAE.

2.3.4 Unforeseeable Risks

A substantial body of evidence already exists on the THS 2.2 and no safety concerns were reported. The possibility of unforeseeable events/risks will be explained again at V10 prior to signing the ICF of the extension study. Non-expected malfunction of THS 2.2 may lead to unforeseeable risks. Subjects will be informed that THS 2.2 is not demonstrated to be less harmful than CC. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Primary Objective and Endpoints

The primary objective of this study is:

1. To determine the changes to the selected clinical risk endpoints ("smokers' health profile") in smokers who have switched from CC to THS 2.2 as compared to those who continued to smoke CC.

   Endpoints included in the "smokers' health profile" measured at V16 (Week 52):

   - High density lipoprotein cholesterol (HDL-C) in serum.
   - White blood cell total count (WBC) in blood.
   - Soluble intercellular adhesion molecule 1 (sICAM-1) in serum.
   - 11-dehydrothromboxane B2 (11-DTXB$_2$) in urine (expressed as concentration adjusted for creatinine).
   - 8-epi-prostaglandin F$_{2\alpha}$ (8-epi-PGF$_{2\alpha}$) in urine (expressed as concentration adjusted for creatinine).
   - Carboxyhemoglobin (COHb) in blood.
   - Forced expiratory volume in 1 second (FEV$_1$ post-bronchodilator, expressed as % predicted [FEV$_1$ %pred]).
   - Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) in urine (expressed as concentration adjusted for creatinine).

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

2. To evaluate self-reported product use (CC and THS 2.2) over the duration of the study.

   Endpoint (measured daily):

   - Number of CC or THS Tobacco Sticks used daily as reported in the self-reported product use electronic diary.

3. To determine the reduction in exposure to HPHCs in smokers who have switched from CC to THS 2.2 as compared to those who continued to smoke CC.

   Endpoints at V16 (Week 52):

   - BoExp to CO: CO in exhaled breath (expressed as ppm).
   - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN) in urine (expressed as concentration adjusted for creatinine).

4. To determine the levels of nicotine exposure in smokers who have switched from CC to THS 2.2 as compared to those who have continued to smoke CC.

   Endpoints (BoExp to nicotine) over the duration of the study:

   - Nicotine equivalent (Neq): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide in urine (expressed as concentration adjusted for creatinine).
   - Nicotine and cotinine in plasma expressed in ng/mL.

5. To describe the changes of biological or functional markers associated with respiratory diseases and cardiovascular diseases (CVD) in smokers who have switched from CC to THS 2.2 as compared to those who have continued to smoke CC.

   Endpoints associated with respiratory diseases measured at V16 (Week 52):

   - Lung function:
     - Spirometry pre- and post-bronchodilator: FEV_1, forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow (FEF 25-75) and bronchodilator reversibility in FEV_1.
     - Lung volume pre-bronchodilator: forced residual capacity (FRC), vital capacity (VC), total lung capacity (TLC), and inspiratory capacity (IC).
   - Cough symptoms (intensity and frequency), amount of sputum production, and bothersomeness of cough symptom from the cough questionnaire.

   Endpoints associated with CVD measured at V16 (Week 52):

   - Myeloperoxidase (MPO), apolipoprotein A1 and B (Apo A1 and Apo B), high sensitivity C-reactive protein (hs-CRP), and low density lipoprotein cholesterol (LDL-C), in serum.
   - Fibrinogen and homocysteine in plasma.
   - Albumin in urine (expressed as concentration adjusted to creatinine).
   - Platelet count and hemoglobin glycosylated (HbA1c in whole blood).
   - Blood pressure, weight, and waist circumference.

6. To describe the changes in subjective effects of smoking in smokers who have switched from CC to THS 2.2 as compared to those who have continued to smoke CC.

   Endpoint over the duration of the study:

   - Product evaluation: subscales from the modified cigarette evaluation questionnaire (MCEQ).

7. To describe the intention to use THS 2.2 in smokers who have switched from CC to THS 2.2.

   Endpoint at V16 (Week 52):

   - Intention to use associated with THS 2.2: item scores from intent to use questionnaire for THS 2.2 (ITUQ) only for subjects in the THS 2.2 arm.

8. To describe the change in tobacco dependence in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoints at V16 (Week 52):

   - Score from the Fagerström (FTND) questionnaire.
   - Time to first cigarette from the FTND questionnaire.

9. To describe the effect of combined product use (dual use) over the study on the components of the "smokers' health profile'.

   Endpoint:

   - The levels of the components in the "smokers' health profile" and the number of CC and THS Tobacco Sticks used daily as reported on the self-reported product use electronic diary.

10. To evaluate the safety profiles associated with THS 2.2 and CC.

    Endpoints over the duration of the study:

    - Adverse events (AEs), serious adverse events (SAEs) and device events, including THS 2.2 malfunction/misuse.
    - Vital signs.
    - Electrocardiogram (ECG).
    - Clinical chemistry, hematology and urine analysis safety panel.
    - Physical examination.
    - Concomitant medications.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This study is a 26 week extension study of the original study (ZRHR-ERS-09-US), a randomized, controlled, open-label, 2-arm, parallel group study design conducted over a 26 week period. This extension study will be conducted as a separate study, as a follow-up of the randomized exposure period of the original study, extending the exposure from V10 (Week 26) to V16 (Week 52), but will be using the same sites. Subjects will continue to use the product they were randomized to in the original study (THS 2.2 arm or CC arm).

The extension study will be an *ad libitum* smoking study with unrestricted product use for the duration of the study (including during site visits).

End of Study for whole study is the last subject individual EOS.

Subjects that terminate the study after enrollment and prior to completion of the extension study will undertake early termination procedures (section 9.4).

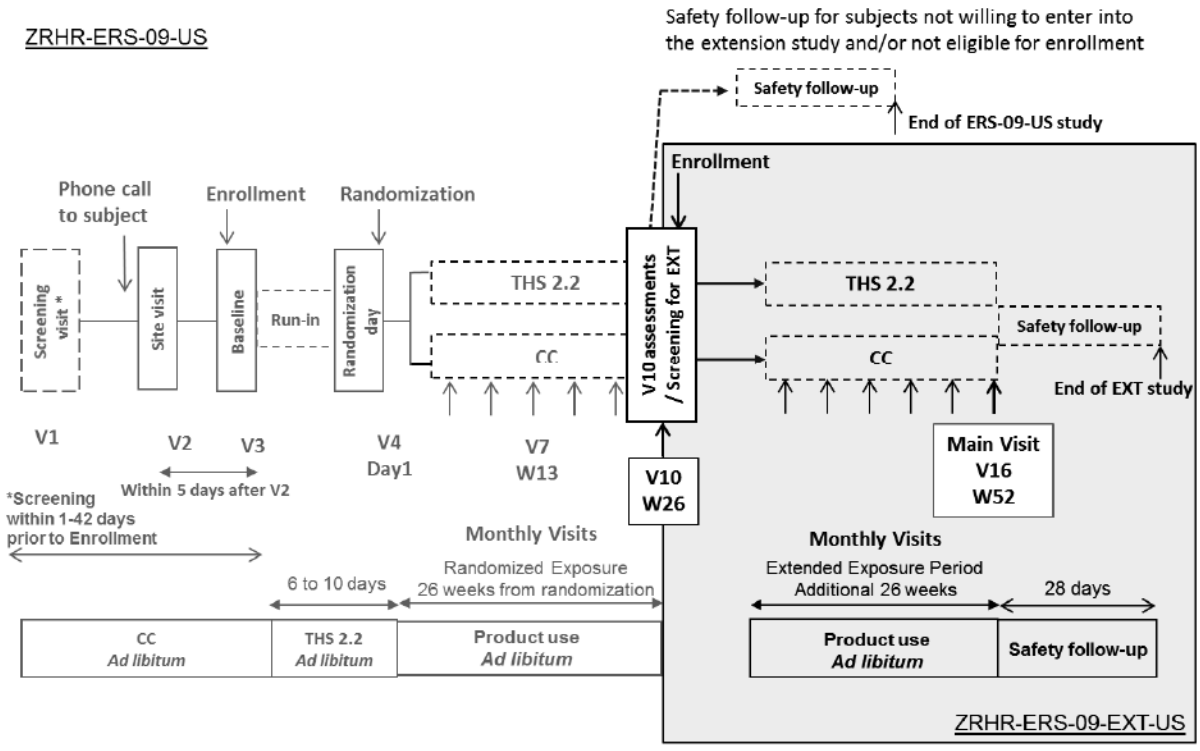


Figure 2 Overall Study Design

The V10 (Week 26): screening and enrollment into the extension

V10 represents both the last visit of the main study as well as the first of the extension study. For subjects willing to participate in the extension study, it also corresponds to the first visit in the extension study. Once all V10 assessments from the original study have been performed, subjects will be offered to enter into the extension study. The enrollment can only take place at V10.

Enrolled subjects will be informed to continue to use the product they were randomized to in the original study as follows:

- THS 2.2 arm: use of THS 2.2 *ad libitum*.
- CC arm: use of their own CC brand *ad libitum*.

Subjects who do not sign the ICF for the extension study at V10, will enter the 28 day safety follow-up period of the original study.

Subjects who sign the ICF for the extension study but do not meet the entry criteria will be considered as screening failure and will enter the 28 day safety follow-up period of the original study. If the subject withdraws or is removed from the study after enrollment, he/she will enter the safety follow up period of the extension study (section 9.3).

The Extended Exposure Period (from Check-out of V10 [Week 26] until Check-out of V16 [Week 52]):

Enrolled subjects will continue to use the product they were randomized to in the original study (THS 2.2 arm or CC arm) in an ambulatory setting for an additional 26 weeks *ad libitum*, including during the visits. Subjects will continue to capture the number of each of the products used including THS Tobacco Sticks, CC (menthol and non-menthol), and other nicotine/tobacco containing products on a daily basis in a product use diary.

After V10, subjects will be required to come for 6 monthly visits to the site for resupply of THS 2.2 (except for V16) and for safety assessments. The visits will be scheduled with a time window of +/- 5 days respective to V4 of the original study:

- V11 (30 weeks after V4, 210 days +/- 5 days),
- V12 (35 weeks after V4, 245 days +/- 5 days),
- V13 (39 weeks after V4, 273 days +/- 5 days),
- V14 (43 weeks after V4, 301 days +/- 5 days),
- V15 (48 weeks after V4, 336 days +/- 5 days),
- V16 (52 weeks after V4, 364 days +/- 5 days).

At V15, containers to collect 24 hour urine will be distributed to the subjects. Twenty four-hour urine collection will start in the morning of the day before V16 and will end 24 hours later on the morning of V16. At V16, blood and urine samples from the 24 hour urine collection will be collected by the site for the assessments of BoExp and clinical risk endpoints.

Any subject, who wants to make a quit attempt from using tobacco-containing products (e.g. THS 2.2 and CC) during the study, will be encouraged to do so and will be referred to appropriate services. The subject will not be discontinued from the study, will come to all scheduled visits for assessments, and his/her financial compensation will not be affected. A subjects in the THS 2.2 arm, who decides to quit using tobacco-containing products (e.g. THS 2.2 and CC), will return all the THS 2.2 components he/she was given during the study and will not be provided with THS 2.2 anymore, starting from the day he/she intends to quit onwards.

The Safety Follow-up Period (from the Check-out of V16 (Week 52) plus 28 days):

At the end of the extended exposure period (i.e., or study completion on V16), subjects will enter into a safety follow-up period for 28 days. During the safety follow-up period, spontaneously reported and ongoing AE/SAEs will be actively monitored by the site. The end of study (individual) is defined as the check-out of the subject on V16 or the date of termination of the subject plus a 28 day safety follow-up period, if applicable. For further information on safety follow-up requirements refer to section 9.3.

4.2 Rationale for Study Design and Control Groups

The extension study will be conducted as a follow-up of the randomized exposure period of the original study extending the exposure from V10 (Week 26) to V16 (Week 52).

In conjunction with the original study, this extension study will:

- Provide a perspective of product usage in a “real world setting” over a 52 week period, where smoking CC in addition to THS 2.2 is expected (dual use).
- Determine the changes in the components of the “smokers’ health profile” upon THS 2.2 use over a 52 week period. A particular interest will be given to FEV_1, one of the endpoints of the “smokers’ health profile”, for which a time frame of 6 months to 3 years is expected to observe a favorable change. Additional clinical risk endpoints involved in the mechanism of smoking-related diseases will be studied to provide additional scientific evidence to strengthen the primary objective.

The “smokers’ health profile” (Table 1), and used as co-primary endpoints in the original study, is a collection of eight, broad-ranging clinical risk endpoints, that together cover the biological processes, physiological systems, and mechanisms of actions that are known to contribute to smoking-related diseases. Many of the clinical risk endpoints included within the “smokers’ health profile” are also mentioned in the 2010 Surgeon General's Report “How

Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease" [5].

Twenty four-hour urine is the standard method to measure the levels of excretion of BoExp and will be collected in this study.

This study is designed as an *ad libitum* study without product use restriction in order to mimic as close as possible "real life" conditions.

4.3 Appropriateness of Measurements

The clinical risk endpoints of the "smokers' health profile" (Table 1) measured in the original and extension studies were selected based on the following criteria: 1) the availability of a validated analytical method; 2) measure is known to be directly or indirectly affected by smoking; 3) measure is readily reversible after smoking cessation/abstinence; 4) timeframe of reversibility of measure in the perspective of the study duration; 5) practicality/acceptability by subjects; 6) robustness of the method (rapid, simple, accurate).

All other clinical risk endpoints or laboratory variables to be measured in these studies were selected based on the following criteria 1) the availability of a validated analytical method; 2) practicality/acceptability by subjects; 3) robustness of the method (rapid, simple, accurate); 4) their clinical relevance to support the primary objective.

For the extension study a subset of BoExp was selected from the list of the original study, including exhaled CO, total NNN and nicotine (Neq in urine, and plasma nicotine and cotinine). Exhaled CO was selected to provide information to CO exposure in addition to COHb, as acute CO exposure is known to be related to cardiovascular diseases. Total NNN was selected based on its specificity to tobacco.

Questionnaires used in these studies are available as validated questionnaires or will be validated before the study will be analyzed (except from questionnaires to assess cough).

4.4 Study Duration

The entire extension study duration per subject will be up to 26 weeks (6 months) plus 28 days of safety follow-up.

5 STUDY POPULATION

5.1 Selection of Study Population

All subjects who have completed the 26 week randomized exposure period (V10) of the original study will be potentially eligible for enrollment into the extension study, depending on whether or not they want to participate and if they meet the entry criteria.

The maximum number of subjects that can be enrolled is pre-defined by the number of subjects completing the 26 week period of the original study. The target population in the original study was approximately 950 female or male, healthy adult smokers. All races/ethnicities were considered eligible, although a quota was applied to subjects of Caucasian origin (Race is White and Ethnicity is Not Hispanic or Latino), as they should not represent more than 75% of the randomized subjects.

5.1.1 Inclusion Criteria

At V10, each subject must meet the following criteria to be eligible to enter in the extension study:

Inclusion Criteria	**Screening at V10**
1. Subject has completed V10 of the original study (ZRHR-ERS-09-US).	X
2. Subject has signed the ICF at V10 and is able to understand the information provided in the ICF.	X
3. The subject is willing to comply to study procedures and to continue to use the product he/she was allocated to during the original study (THS 2.2 or CC) for an additional 26 weeks.	X

5.1.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must not be enrolled into the study:

Exclusion Criteria	**Screening at V10**
1. As per judgment of the PI(s) or designee(s), the subject cannot participate in the study for any reason (e.g. medical, psychiatric and/or social reason).	X

Exclusion Criteria	Screening at V10
2. Any medical conditions that in the opinion of the PI(s) or designee(s) would jeopardize the safety of the participant.	X
3. Subject has made a quit attempt* during the original study.	X
4. For women only: Subject is pregnant (does not have a negative pregnancy test at V10) or is breast feeding.	X
5. For women only : Subject does not agree to use an acceptable method of effective contraception**.	X

* From using tobacco-containing products (e.g. THS 2.2 and CC). This information will be captured from the original study.

** *e.g.*, Intrauterine device, intrauterine system, established use of oral/injectable/implantable/transdermal hormonal methods, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from V10 until V16. Hysterectomy, tubal ligation, bilateral oophorectomy or post-menopausal status are reasons for not needing to use birth control. Post-menopausal status is defined as women who have not experienced menses for greater than 12 months.

5.2 Discontinuation of Subjects from the Study

Discontinued subjects will include both subjects who withdraw from the study (subject's decision) or subjects who are removed from the study. A subject can only be discontinued from the study after enrollment.

Subjects will be informed that they are free to withdraw from the study (upon decision of the subject) at any time. Subjects should be questioned for the reason for withdrawal from the study, although they are not obliged to disclose it. If the subject withdraws from the study he/she will be asked to confirm at least the following points and this information will be fully documented by the PI(s) or designee(s):

- If applicable, the subject still consents for long-term biobanking (2 ICFs).
- Whether the subject requested withdrawal of Health Insurance Portability and Accountability Act (HIPAA) authorization.
- The subject agrees to undertake the early termination procedures (section 9.4).

When a subject is discontinued from the study, early termination procedures (section 9.4) are performed within a period of 5 days after the discontinuation date unless the subject refuses to perform the assessments. After the date of early termination visit, the subject will enter into

the 28 day safety follow-up period. In case an early termination visit is not performed, the subject will still enter into the 28 days Safety Follow-up period after the discontinuation date.

Subjects must be discontinued from the study for any of the following reasons:

- Withdrawal of informed consent.
- Any AE or condition (including clinically relevant changes in a laboratory parameter), which at the discretion of the PI(s) or designee(s) no longer justifies the subject's participation in this study.
- Positive pregnancy testing (section 8.5).
- The Sponsor or PI(s) or designee(s) terminates the study or the study terminates at a particular site. If the Sponsor or the PI(s) or designee(s) decides to prematurely terminate the study, the subject will be promptly informed. The PI(s) or designee(s) should report the fact and the reason in writing to the IRB.
- Discontinuation is considered to be in the best interest of the subject or the other subjects as judged by the PI(s) or designee(s).

Subjects may be discontinued from the study for the following reason:

- Non-compliance to the study procedures based on the judgment of the PI(s) or designee(s).

Use of any tobacco/nicotine containing product different from the allocated product during the extended exposure period, will not lead to the discontinuation of the subject from the study.

Subjects that discontinue the study after enrollment will not be allowed to re-enter the study.

5.3 Lost to Follow-up

The date of the last contact with the subject (e.g. last visit, last phone call) should be recorded in the source document.

After the last contact, reasonable number of attempts to contact the subject (including written correspondence and phone calls) should be done and documented in the source documents by the site.

Following the contact attempts, if the PI(s) or designee(s) decides to discontinue the subject with the reason of lost to follow-up, the discontinuation date will be recorded. The discontinuation date for the subject will be the date the subject was determined to be lost to follow-up and will correspond to the date of the end of study of the subject. If the site has lost track of the subject, the discontinuation date cannot exceed the maximum number of study days (XX), then the PI(s) or designee(s) will discontinue the subject with reason as lost to follow-up.

5.4 Violation of Selection Criteria

Any subject who is willing to participate in the extension study but do not meet the entry criteria of the extension study after signing the ICF at V10 will be considered as screening failure and will enter in the 28 day safety follow-up period of the original study.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

6.1.1 Test Product

THS 2.2 comprises the following components: a THS Tobacco Stick, a Holder, a Charger, a Cleaning Tool, a power supply, and a USB cable (see the user guide - Appendix 4):

Charger:	The function of the Charger is to recharge the Holder after use. It contains a battery with sufficient capacity to recharge the Holder for approximately 20 times.
THS Tobacco Stick Holder (Holder):	The function of the Holder is to heat the THS Tobacco Stick and to deliver an aerosol to the user. The electrical heating is powered from an internal battery, which delivers power for about 6 minutes (allowing complete use of a single THS Tobacco Stick).
THS Tobacco Stick (Tobacco Stick):	The THS Tobacco Stick contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder.

The overall objective of the product design is to provide an acceptable alternative to current, adult smokers, in which the exposure to HPHCs in the aerosol is substantially reduced in comparison with CC.

THS 2.2 will be provided by the Sponsor.

6.1.2 Reference Product / Baseline Product

The subject's own preferred brands of CC will be used as the reference product to THS 2.2. There will be no CC brand restriction. CCs will not be provided nor reimbursed by the Sponsor.

6.1.3 Packaging and Labeling

For the THS Tobacco Sticks, the packs and cartons will be labeled "for investigational use only" and according to any additional local regulatory requirements.

6.2 Use of Investigational Products

Subjects will not be requested or forced to smoke CC or to use THS 2.2 and will be free to stop using their allocated product (THS 2.2 or CC) at any time during the study. THS 2.2 will not be promoted for commercial distribution or test market.

6.2.1 Extended Exposure Period

Subjects will be instructed to use exclusively the product they were randomized to in the original study (THS 2.2 arm or CC arm) from check out of V10 until check out of V16. The use of THS 2.2 and CC will be allowed on site based on arm allocation. At the check-out of each ambulatory visit, subjects in the THS 2.2 arm will be instructed to continue using exclusively THS 2.2 until the check-out of V16.

For subjects in the THS 2.2 and CC arms, the use of other tobacco/nicotine containing products will be allowed including during the visits. However, for subjects in the CC arm, the use of THS 2.2 will not be allowed.

From V10 to V15, enrolled subjects in the THS 2.2 arm will be provided with a sufficient amount of THS Tobacco Sticks to cover their needs until the next visit; they will be requested to bring back THS 2.2 components including the unused and partially used packs of THS Tobacco Sticks at each ambulatory visit.

Any subject, who wants to make a quit attempt from using tobacco-containing products (e.g. THS 2.2 and CC) during the study will be encouraged to do so and will be referred to appropriate services. The subject will not be discontinued from the study, will come to all scheduled visits for assessments, and his/her financial compensation will not be affected. Subjects in the THS 2.2 arm who decide to quit using tobacco-containing products (e.g. THS 2.2 and CC) will not be provided with THS 2.2 anymore, starting from the day they intend to quit onwards.

6.2.2 Stopping Rules for Investigational Product

For safety purposes, smoking and THS 2.2 use should be temporarily stopped in the event of any signs suggesting nicotine overexposure, (*e.g.*, gastrointestinal disturbance [nausea, vomiting, diarrhea, stomach or abdominal pain], cold sweats, headache, dizziness, and breathing problems) or any reasons at the discretion of the PI(s) or designee(s). If the study product is discontinued, the reasons for discontinuation will be documented in the source documents and subjects will undertake early termination procedures (section 9.4).

6.2.3 Safety Follow-up Period

There will be no restrictions of CC use during the safety follow-up period.

6.3 Method for Assigning Subjects to Study Arms

During the extension study, subjects will remain in the study arm they were randomized to in the original study (THS 2.2 arm or CC arm in a 1:1 ratio).

Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS).

6.4 Blinding

This is an open-label study; the subjects and PI(s) or designee(s) were unblinded to the subject's study arm after randomization at V4 during the original study.

However, and similarly to the original study there will be a limited degree of blinding during the conduct of the extension study, including the data review and data analysis process. In particular, some members of PMI and contract research organization (CRO) personnel will be blinded as summarized in Table 2:

Table 2 Blinding Scheme

Blinded Study Personnel	Blinded Data	End of Blinding Period
PMI and Covance study statisticians	Actual values of primary endpoints at V16[1]	After the SAP finalization or database lock, whichever comes last
PMI clinical scientist	Actual values of primary endpoints at V16[1]	After the finalization of PMI blind database review[1]. Can be actively un-blinded when appropriate.

1 To avoid indirect unblinding of the "actual values of primary endpoints" additional data were blinded in the eCRF (e.g. adverse event terms). After SAP finalization or database lock of the original study, whichever comes last, the whole study team will be unblinded to all data collected in the original study, following the process described in the original study protocol.

2 As part of the PMI Quality Control (QC) activity, data listings will be reviewed by Covance and PMI before database lock. Full details will be available in the data review plan.

Any PMI and CRO personnel who are not listed in the above Table 2 will be unblinded by default.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period (Table 2). 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 within or to a subject. Unblinded data will only be reviewed by the unblinded study team.

6.5 Investigational Product Accountability and Adherence

6.5.1 Dispensing Investigational Product

CC:

- From ICF signature at V10 to the end of the study, subject will use their own preferred brand of CC *ad libitum*.

THS 2.2:

- During the extended exposure period: subjects in the THS 2.2 arm will be provided with anticipated amount of THS Tobacco Sticks to cover the period until the next study visit. In the situation in which a subject needs more THS Tobacco Sticks, extra visits may be scheduled.

6.5.2 Storage and Accountability

No accountability will be done for the CC arm.

A person in the site staff designated by the PI(s) or designee(s) will be responsible for the storage and accountability of THS 2.2 components and THS Tobacco Sticks, in accordance with the Sponsor's requirements.

The THS 2.2 components and THS Tobacco Sticks will be stored in a secured storage site within storage specifications with access limited to authorized personnel only. Full accountability of THS 2.2 will be ensured by the designated site staff by recording the timing and quantities of distribution of THS 2.2 components and THS Tobacco Sticks in appropriate logs at each visit.

6.5.3 Investigational Product Retention

No retention will be done for CC.

The study site will return to the Sponsor any unused and partially used packs of THS Tobacco Sticks and THS 2.2 components upon study completion or as required. Retention of THS 2.2 will be documented in an appropriate log.

6.5.4 Adherence to Investigational Product

From enrolment until V16, the adherence of subjects in the 2 study arms will be based on the daily self-reporting of the subject in the product use electronic diary (section 7.7.1).

6.6 Restrictions

6.6.1 Smoking Restrictions

To avoid cross-contamination among the 2 study arms subjects will be allowed to use IP in areas dedicated to CC or THS 2.2 use during the visits at the site. These product use areas could be organized outdoor. On each visit, smoking and product use will be allowed except during procedures at the discretion of the site. In general, the performance of scheduled procedures has priority over the wish of a subject to use the product.

Except for the subjects in the THS 2.2 arm, subjects will not be allowed to use THS 2.2 during the extended exposure period.

6.6.2 Dietary Restrictions

Subjects will not be allowed to bring their own food or beverages to the site. During the visits, meals and light snacks, fruits and raw vegetables can be distributed to the subjects without restrictions at any time during the visit. Consumption of water will be allowed as desired.

Fasting state has to be observed for at least 10 hours prior to blood draws at V16 for:

1. Safety laboratory parameters.
2. Clinical risk endpoints except COHb.
3. Serum/plasma biobanking samples for further analysis of BoExp and clinical risk endpoints.
4. Blood biobanking for transcriptomics and lipidomics.

6.7 Concomitant Medications

Medications will be allowed during the study and will be carefully monitored by the PI(s) or designee(s). The PI(s) or designee(s) is (are) responsible for the medical care including medication of the subjects during their participation in the study. Any decisions regarding the prescription of medications will be made in the best interest of the subject. All concomitant medication ongoing at V10 will be followed up during the extension study. Any use of concomitant medication must be fully documented in the source document and recorded into the case report form (CRF) (section 7.3.1).

Any concomitant medication (Appendix 2) which has a potential impact on the "smokers' health profile" including the use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (including over-the counter products) should be avoided and carefully considered especially when they will be taken prior to V16, as they could interfere with clinical risk endpoints such as 11-DTX-B_2 (the last dose of the concomitant medication should be at least 5 half-lives prior to V16). In case drugs/short-and long-term vitamins listed in Appendix 2 are taken by the subject during the extension study, they will be recorded as concomitant medications (except when salbutamol is used for post-bronchodilator spirometry testing), and this will not be a reason to discontinue the subject from the study. Appendix 2 provides an overview of selected concomitant medication and their potential impact on clinical risk endpoints. Medications containing estrogens (*i.e.* for contraception and for hormone replacement therapy), will be allowed in this study and must be recorded in the CRF.

7 STUDY PROCEDURES

Personnel performing study assessments must have the appropriate and fully documented training. If the personnel changes during the study, a new fully documented training must be scheduled. An overview of all study assessments is shown in the schedule of events (Appendix 1). Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care. Site personnel will adhere to the site's standard operating procedures (SOPs) for study related procedures.

7.1 Informed Consent

The subject will be asked to provide his/her written consent to participate to the extension study (ICF for study participation) at the end of V10, after all the assessments of the original study are completed (section 1.3). The V10 assessments of the extension study can start only once the subject has signed the ICF.

In addition to the ICF for the extension study participation, only subjects who have previously provided consent for biobanking (and did not withdraw it) will be asked to provide his/her separate optional consent at V10 for the further collection of samples and storage for long-term biobanking at V16 (section 1.3.2):

- ICF for the additional biobanking of serum/plasma/urine samples for further measurements of BoExp and clinical risk endpoints.
- ICF for the additional biobanking of blood sample for further transcriptomics and lipidomics analysis/sample collection.

The subject's participation to the study does not depend on his/her consent for biobanking and will be separated from that for study participation. The additional consents will be captured in the CRF.

7.2 Information on the Risk of Smoking and Smoking Cessation Advice and Debriefing

At each visit from V11 to V16: each subject will be given during the same session 1) information on the risks of smoking, 2) smoking cessation advice, and 3) debriefing on THS 2.2 according to Appendix 1.

The information on the risk of smoking and the advice on smoking cessation will take the form of a brief interview according to the recommendations of the Public Health Service [33, 34]. The debriefing of subjects on THS 2.2 will address any intended or unintended beliefs that participants may have about THS 2.2. The goal of the debriefing is to help ensure that subjects exit the study with an accurate understanding of the product risks, including an understanding that THS 2.2 has not been demonstrated to be less harmful than CC.

Details of the sessions will be recorded in the source document file. These sessions will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the PI(s) or designee(s), and may additionally be given in a group session.

7.3 Clinical Assessments

All assessments of the extension study will be performed in the same standardized way as in the original study to ensure homogeneity of data collection. During the original study demographic data was recorded and subjects were asked questions about their smoking history and habits.

7.3.1 Concomitant Disease, Previous and Ongoing Medications

A concomitant disease is defined as any clinically relevant medical condition that was either detected at V1, and/or was still ongoing at V1. Any untoward medical occurrence in a subject detected during the original and the extension studies, which was not present at V1 of the original study, must be documented as an AE. Worsening of a pre-existing condition from V1 onwards will also be documented as an AE.

All concomitant medication taken during the extension study (from enrolment at V10 to V16) will be documented in the source documents and recorded in the CRF of the extension study. Medication which is ongoing at V10 will be considered as a concomitant medication in the extension study. This applies to both prescription and over-the-counter products.

Records of medication taken include the drug name (preferably both generic and trade name), route of administration (*e.g.*, oral, intravenous), total daily dose/unit (*e.g.*, expressed in mg, mL, or IU), indication, the frequency, the start and (if applicable), the stop date (day, month and year). Any therapy changes (including changes of regimen) during the study are to be documented.

7.3.2 Physical Examination

Physical examination will be performed according to Appendix 1.

7.3.3 Body Height, Weight and Waist Circumference

Body height was recorded during the original study at V1.

Body weight will be recorded according to Appendix 1.

Waist circumference will be recorded according to Appendix 1.

BMI will be calculated at V13 and V16 from the height (recorded at V1) and body weight recorded at V13 and V16 using the following formula:

$$BMI = \frac{\text{weight in kilograms}}{\text{height in meters}^2} \quad (kg/m^2)$$

Weight and waist circumference will also be analyzed as CVD clinical risk endpoints.

Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

7.3.4 Vital signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate will be recorded according to Appendix 1. All measurements will be made after the subject has rested for at least 5 minutes in a supine position.

7.3.5 Other Clinical Assessments

7.3.5.1 Lung Function Testing

All personnel performing lung function testing must have the appropriate training. In addition QC measures should be put into place and be properly documented and filed at the pulmonary function laboratory (including the records of the calibration, if applicable). A certified study site staff should perform the assessment and the results will be assessed by a pulmonologist. The subject will be at rest for at least 15 minutes prior to lung function testing. All lung function manoeuvers will be recorded with the subject in a sitting position throughout the study.

All lung function tests will be managed by a central provider, including the provision of equipment and site manual.

All lung function data will be reviewed by blinded over-readers and the acceptability of the overall sessions and individual tests will be provided to the Investigator.

At the end of each appropriate visit the certified study site staff will be required to send the lung function data to the central provider.

Spirometry Testing

The spirometry test will be performed in accordance with the 2005 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry [35]. Spirometry predicted values will be standardized to the Third National Health and Nutrition Examination Survey (NHANES III) predicted set.

The spirometry tests will include the recording of FEV_1, FVC, FEV_1/FVC ratio and FEF 25-75.

All spirometry tests will be performed using the multi-breath (closed circuit) technique, as described in the Investigator pulmonary function testing (PFT) site manual. The PFT manual will include information on equipment, procedures, subject instructions and precautions.

All spirometry tests must be performed 1 hour after smoking or using THS 2.2.

Each subject will need to begin their spirometry tests in a time window of +/- 2 hours respective to the time of the spirometry tests done at V3 (Baseline) during the original study.

Pre- and Post-Bronchodilator Spirometry Testing:

- At V16:

Pre- and post-bronchodilator spirometry test will be performed. Values for FEV_1, FVC, and FEF 25-75 will be recorded. The ratio FEV_1/FVC will be calculated from the highest acceptable FEV_1 and the highest acceptable FVC respectively. At V16, pre- and post-bronchodilator spirometry will be used to describe the changes in pre- and post-bronchodilator spirometry measurements over the duration of the study.

All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of around 400 µg of salbutamol (usually equivalent to 4 puffs assuming 100 µg/puff). The time of salbutamol inhalation and time of spirometry assessment will be recorded in the source document.

At V16, in case the value of the pre- and post-bronchodilator spirometry test(s) do not meet the ATS/ERS criteria the subject will need to come back within a 7 day window to repeat the test(s).

Lung Volume Measurements Using Multiple Breath Helium Dilution Technique:

At V16: lung volume measurements will be conducted as part of the lung function tests and the following values will be recorded: VC, functional residual capacity (FRC), IC and TLC. If required, a second test can be performed. Between tests, a minimum waiting time of 4 minutes is required. For FRC, the mean value will be used if more than one attempt is performed. TLC is evaluated as FRC plus IC. VC will be the highest from FRC-He if more than one attempt is performed. RV will be calculated as TLC minus VC_{max}. VC_{max} is the highest from FRC-He wash in.

All lung volumes measurements will be done pre-bronchodilator as outlined in Appendix 1. The PFT manual will include information on equipment, procedures, subject instructions and precautions.

The helium dilution technique will be used in accordance with the recommendations of the ATS/ETS Joint Task Force on the standardization of the measurement of lung volumes [36]. This technique is a closed-circuit system where a spirometer is filled with a mixture of helium

and oxygen. The closed-circuit rolling seal spirometer will be filled to a starting volume of six liters with a mixture of containing helium, oxygen and balance room air. Oxygen will be set to 30% so that all test subjects will be comfortable; exact contents will be analyzed. The subject will be asked to seal their lips around the mouthpiece and breathe normally on the closed-circuit while the helium mixes and equilibrates. During this time carbon dioxide will be removed by a chemical absorber and oxygen will be automatically replaced. Once equilibration has occurred, the subject will be asked to perform one or more vital capacity efforts to end the test.

7.3.5.2 Electrocardiogram

ECG testing will be performed as per the site's local practice according to Appendix 1. A standard 12-lead ECG will be recorded after the subject has rested for at least 5 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QT interval corrected according to Bazett's formula and Fridericia's formula. Every ECG has to be assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis has to be provided on the CRF for all ECGs assessed as abnormal – clinically relevant. All ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents and signed by the PI(s) or designee(s).

7.4 Biomarker Assessment

All bioanalytical assays and laboratory assessments will be carried out using validated methods (sections 7.5 and 7.6) according to the laboratory manual. The bioanalytical methods used will be documented in the respective bioanalytical plans/reports. A list of laboratories is provided in Appendix 2.

All assessments of the extension study will be performed in the same standardized way as in the original study to ensure homogeneity of data collection.

7.4.1 Clinical Risk Endpoints Related to Cardiovascular Diseases

7.4.1.1 HDL-C, s-ICAM-1, Apo A1 and B, MPO, LDL-C, and hsCRP in serum

A blood draw for each assay will be collected at this time point according to Appendix 1.

HDL-C and s-ICAM-1 will be evaluated as part of the "smokers' health profile."

7.4.1.2 Fibrinogen and Homocysteine in Plasma

A blood draw for each assay will be collected according to Appendix 1.

7.4.1.3 Carboxyhemoglobin and Hemoglobin Glycosylated A1c in Whole Blood

A blood draw for each assay will be collected irrespective of product use. COHb will be evaluated as part of the "smokers' health profile." according to Appendix 1.

7.4.1.4 11-DTX-B_2 / 8-epi-$PGF_{2\alpha}$, and Albumin in Urine

Sampling from 24-hour urine collection to measure 11-DTX-B_2, 8-epi-$PGF_{2\alpha}$ and albumin. The results will be normalized to creatinine and expressed as concentration adjusted for creatinine. 11-DTX-B_2 and 8-epi-$PGF_{2\alpha}$ will be evaluated as part of the "smokers' health profile". The albumin to creatinine ratio will be used to evaluate potential microalbuminuria according to Appendix 1.

7.4.2 Clinical Risk Endpoints Related to Genotoxicity

Sampling from 24-hour urine collection to measure total NNAL according to Appendix 1. The results will be normalized to creatinine and expressed as concentration adjusted for creatinine. Total NNAL will be evaluated as part of the "smokers' health profile."

7.4.3 Biomarker of Exposure

7.4.3.1 Biomarkers of Exposure to CO:

The CO breath test should be conducted in timely conjunction with the blood sampling for COHb where applicable.

CO Breath Test: CO in exhaled breath will be measured using the Smokerlyzer® device, such as the Micro 4 Smokerlyzer® device or similar in the 2 study arms.

Once a day according to Appendix 1.

7.4.3.2 Plasma Nicotine and Cotinine in Plasma

One blood draw will be collected for the measurement of nicotine and cotinine according to Appendix 1. The levels of nicotine and cotinine will be described over the duration of the study.

7.4.4 Other Biomarkers of Exposure

The following BoExp will be measured in 24-hour urine collection: total NNN and Neq according to Appendix 1. The results will be normalized to creatinine and expressed as concentration adjusted to creatinine.

7.4.5 Creatinine

Creatinine will be measured for normalization of urinary BoExp (total NNN, total NNAL and Neq) and urinary clinical risk endpoints (11-DTX-B_2, 8-epi-$PGF_{2\alpha}$, albumin and total NNAL) according to Appendix 1 .

7.5 Laboratory Assessments

All laboratory assessments of the extension study will be performed in the same standardized way as in the original study to ensure homogeneity of data collection.

7.5.1 Clinical Chemistry, Hematology, and Urine Analysis for the Safety Panel

Hematology, clinical chemistry and urine analysis for the safety panel will be measured according to Appendix 1.

Blood samples will be taken after at least 10 hours of fasting (section 6.6.2). The urine test will be performed semi-quantitatively as a urine test. Parameters to be measured are listed in Table 3. Total count of WBC will be evaluated in blood as part of the "smokers' health profile."

Table 3 Clinical Laboratory Parameters for Safety Panel

Hematology	Clinical Chemistry	Urine analysis
• Hematocrit • Hemoglobin • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count* • White blood cell (WBC) count* • Differential WBC count: - Neutrophils - Basophils - Eosinophils - Lymphocytes - Monocytes	• Albumin • Total protein • Alkaline phosphatase (AP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Creatinine • Gamma-glutamyl transferase (GGT) • Glucose • Lactate dehydrogenase (LDH) • Potassium • Sodium • Total bilirubin • Direct bilirubin • Total cholesterol (TC) • Triglycerides (TG)	• pH • Bilirubin • Glucose • Nitrite • Red blood cell traces • Protein • Specific gravity

*RBC and WBC morphology tests might be performed in case of abnormal values.

7.5.2 Urine Pregnancy Testing

A pregnancy test will be done on all female subjects according to Appendix 1.

Female subjects with a positive pregnancy test at V10 will not be offered to enter in the extension study and the PI(s) or designee(s) will inform those subject about the risks associated with smoking during pregnancy. All pregnancies detected during the study must be reported and handled as described in section 8.5.

7.6 Sampling Handling and Storage

All blood samples will be tested in one of the two central laboratories (Appendix 3). The pregnancy tests will be done by the personnel at the study sites.

Detailed procedures for sample collection and handling of samples are described in the laboratory manual. Safety laboratory samples will be destroyed as per the laboratory's standard procedures. For the other samples (except biobanking samples), at least one tube per timepoint and per subject should be kept at least up until the finalization of the bioanalytical reports and the database is locked unless the stability for analysis is exceeded.

The bioanalytical laboratory(ies) are listed in Appendix 2.

7.6.1 Blood Samples

Venous blood samples will be collected by qualified and trained site personnel. Subjects should be in a seated position during blood collection.

The maximal total volume of blood drawn for each subject for the extension study at V16 will be around 80 mL, which includes 13 mL for safety and repeated analysis, 10 mL of blood for long-term storage of the biobanking samples for further analysis of BoExp and clinical risk endpoints (only if additional consent is given at V10) and 9 mL for long-term storage of the biobanking samples for further analysis of transcriptomics and lipidomics (only if additional consent is given at V10) (section 7.6.3).

7.6.2 Urine Samples

Spot urine samples will be used for urine pregnancy test and safety urine analysis for each visit.

24-hour urine collection: the day before the visit, subjects will start collection of his/her 24-hour urine. Subjects will discard their first void in the morning. The collection period will start immediately after. After 24-hours ± 1h of urine collection, subjects will empty their bladder again in the morning of the visit and this urine will be used as the final portion of the 24-hour urine sample. During the collection period, all urine passed must be collected and put into the sampling container. No urine should be passed into the toilet. The start and the end time of

urine collection will be recorded by the subject and checked by the site staff. The volume of 24-hour urine will be measured by the site staff upon collection of urine containers from the subjects. For assessment of urine BoExp, creatinine, 8-epi-$PGF_{2\alpha}$ and 11-DTX-B_2, albumin, and for sample biobanking, aliquots from the 24-hour urine collection will be taken. In the schedule of events (Appendix 1) for the 24-hour urine collection, the dot corresponds to the day on which the 24-hour urine collection period ends.

The 24-hour urine collection will be collected according to Appendix 1

7.6.3 Long-Term Storage (Biobanking)

The facility at which the samples are stored will follow their procedures for destruction of banked samples if a subject withdraws his/her consent for long-term biobanking.

7.6.3.1 Long-Term Storage of Serum/Plasma or Urine

If a subject gives additional consent during V10 for sample biobanking for further analysis of BoExp and clinical risk endpoints, additional samples of urine from the 24-hour collection and serum/plasma will be collected at V16 as follows:

- Samples will be collected from the 24-hour urine collections that started one day before V16 and ended at V16 (5 tubes of 10 mL each).
- Serum/plasma will be collected at V16 (10 mL of blood draw in total). This is to obtain and store 2X 1 mL of serum and 2X 1 mL of plasma.

If a subject gives additional consent during V10 for sample biobanking of whole blood for further transcriptomics and lipidomics analysis, blood will be collected at V16 as follows:

- Blood will be collected for transcriptomics at V16 (5 mL in total). The 5 mL will be split into two tubes of 2.5 mL of whole blood each.
- Plasma will be collected for lipidomics at V16 (4 mL in total). The 4 mL will be split into two tubes of around 500 µl plasma each.

The blood samples for transcriptomics and lipidomics and the data related to these samples will be anonymized and will be the subject of a separate report. Anonymized data and samples are initially single or double coded where the link between the subjects' identifiers and the unique code(s) is subsequently deleted. This is applicable for the blood/plasma biobanking for transcriptomics and lipidomics only.

The samples intended for sample biobanking will be kept frozen; and will be shipped to a central storage facility according to the laboratory manual. After the final the clinical study report (CSR) is signed, samples of plasma/serum/blood will be stored for a maximum of

5 years and samples of urine will be stored for a maximum of 2 years. The blood biobanking for transcriptomics and lipidomics will be stored for a maximum of 5 years.

7.7 Other Study Procedures

7.7.1 Product Use Diary

The subject will capture the number of THS Tobacco Sticks, CCs (menthol and non-menthol), and other nicotine/tobacco containing products used on a daily basis in a product use diary from enrollment until the check-out of V16 (including during the visits). Subjects were trained by site staff on the use of this diary during the original study. The product use diary was supplied by Sponsor and distributed to the subjects by the study site personnel during the original study. If paper diary is used, the subjects will receive instructions from the site staff on how the diary should be completed.

The site will schedule at each visit the next appointments at site in the electronic diary.

7.7.2 Questionnaires

The subject questionnaires and the visual analog scale (VAS) used in this study will be entered by the subject directly in an electronic diary or on paper copy. If a paper copy is used, the VAS scale must be of 100 mm. All subject reported outcome material will be provided in English or Spanish and instructions will be provided in the subject's local language.

7.7.2.1 Fagerström Test for Nicotine Dependence Questionnaire

Subjects will complete themselves the FTND questionnaire according to Appendix 1 in its revised version [37] irrespective of the time of product use.

The questionnaire consists of six questions. The scores obtained on the test permit the classification of nicotine dependence into three levels: mild (0-3 points), moderate (4-6 points), and severe (7-10 points) [37].

7.7.2.2 Cough Questionnaire

Subjects will complete themselves the respiratory symptom "cough" on a VAS, on three Likert scales, and with an open question irrespective of the time of product use according to Appendix 1.

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 VAS, 3 Likert scales, and to answer the open question. On the VAS, subjects will assess how bothersome their cough was during the previous 24 hours. The VAS ranges from "not bothering me at all" to "extremely bothersome".

Furthermore, subjects will assess the intensity and frequency of cough and the amount of sputum production during the previous 24 hours on Likert scales.

- The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = very mild – 2 = mild – 3 = moderate – 4 = severe – 5 = very severe.
- The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = rarely – 2 = sometimes – 3 = fairly often – 4 = often – 5 = almost always.
- The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3, with 0 = no sputum – 1 = a moderate amount of sputum – 2 = a larger amount of sputum – 3 = a very large amount of sputum.

Symptoms or worsening of symptoms documented in the VAS do not need to be documented as additional AEs because the VAS will be analyzed as part of the final report. However, it is at the discretion of the PI(s) or designee(s) to decide whether to document such symptoms as additional AEs. The main source for AE collection will be the face-to-face interview between the subject and study site staff, using open, non-directive questions (section 8.2).

7.7.2.3 Modified Cigarette Evaluation Questionnaire

Subjects will complete themselves the modified cigarette evaluation questionnaire (MCEQ) [38] according to Appendix 1 .

The MCEQ assesses the degree to which subjects experience the reinforcing effects of smoking, by measuring:

- Smoking satisfaction (satisfying, tastes good, and enjoys smoking).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nauseous).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

7.7.2.4 Intention to Use THS 2.2 Questionnaire

Subjects in the THS 2.2 arm will complete themselves the questionnaire on their intention to use THS 2.2 using the ITUQ according to Appendix 1. The ITUQ comprises two sets of items:

- 1 item assessing intention to use THS 2.2 on a regular, ongoing basis to be rated on an ordinal scale with 6 timeframe categories. Only subjects who provide answer different from “definitely not” to this item will be asked to answer the next 6 items.

- 6 items assessing several intentions to use THS 2.2 on a regular, ongoing basis to be rated on a 6-point scale ranging from “definitely not” to “definitely” with higher scores indicating greater likelihood to use THS 2.2.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

The FDA MRTP guideline [4] specifies this definition towards tobacco products, as follows: "An AE is any health-related event associated with the use of a tobacco product in humans, which is adverse or unfavorable, whether or not it is considered tobacco-product related".

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as, but not limited to, any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

Any pre-planned hospitalizations that are known at the time of signing the ICF will not be recorded as SAEs, however they will be recorded as AEs only. Any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

8.2 Assessment of Adverse Events

The PI(s) or designee(s) is (are) responsible for obtaining, assessing, and documenting all AEs during the study.

8.2.1 Collection of Information

Adverse event information will be collected from the time of signature of the ICF at V10 onwards until the end of the extension study for the subject either by the PI(s) or designee(s) via spontaneous reporting or by the use of consistent, open, non-directive questions from study site staff (*e.g.*, "Have you had any health problems since the previous visit/How are you feeling

since you were last asked?"). At the discretion of the PI(s) or designee(s), the collection of AE information may also be triggered from the review of the subject questionnaires and the VAS. However, during the visits, the main source for AE collection will be face-to-face interview(s) with the subject.

Information recorded will include: verbatim description of the AE, start and stop dates and times, seriousness, severity (intensity), action taken (*e.g*., whether or not the AE led to the subject's withdrawal from the study), and outcome (*e.g*., resolved, withdrawal due to AE).

For each AE, the intensity will be graded on a 3-point intensity scale (mild, moderate, severe) using the definitions provided in section 8.2.3.

Any exacerbation/worsening or increased frequency of an AE or pre-existing condition shall be evaluated and recorded.

Correct medical terminology/concepts are preferred when recording AE terms, and abbreviations must be avoided. Wherever possible, a diagnosis is to be used to describe an AE as a diagnosed medical condition rather than individual signs and symptoms (*e.g*., record "pneumonia" rather than "fever", "cough", "pulmonary infiltrate" or "septicemia" rather than "fever" and "hypotension" following blood sample).

Any AE that meets the serious criteria must be recorded both on the AE report form of the CRF and on a separate SAE report form (section 8.3).

8.2.2 Period of Collection

From the time of signature of the ICF of the extension study (at V10) until the end of the study (EOS), all AEs (includes SAEs) will be collected by the study site staff as described below. Any AE ongoing at V10 will be followed up during the extension study.

8.2.2.1 From Enrollment until the End of the Study

Any new, clinically relevant, abnormal finding or worsening of a pre-existing condition/concomitant disease detected during the study including the safety follow-up period will be documented as an AE and/or SAE.

During the safety follow-up period spontaneously reported AEs and/or SAEs will be recorded in the CRF. Any AEs/SAEs ongoing during the 28 day safety period will be actively followed up by the PI(s) or designee(s) until they have been resolved, stabilized (*i.e.,* no worsening of condition), or until an acceptable explanation has been found.

Upon/after the end of the safety follow-up period for all ongoing AEs, the PI(s) will refer the subject to his General Practitioner for follow up of those AEs (section 8.3) until they have been resolved, stabilized (*i.e*., no worsening of condition), or until an acceptable explanation has been found. All ongoing SAEs at the end of the study will be followed up by the PI(s).

8.2.3 Intensity of Adverse Event

For each AE, the intensity will be graded by the PI(s) on a 3-point intensity scale (mild, moderate, severe) using the following definitions:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and requires medical intervention.

According to CIOMS (Council for International Organizations of Medical Sciences) VI Working group, changes in severity (Intensity) and maximum intensity of AEs must be documented.

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

It is difficult to establish a firm method to distinguish an adverse reaction (that is AE that is causally related to the IP) from a clinical adverse event that is temporally associated to the use of an IP.

In general, all AEs and/or SAEs will be assessed by the PI(s) or designee(s) as either "related" or "not related" to IP as described below. In addition to the assessment of the relationship of the clinical event to the IP, the PI(s) or designee(s) shall document a potential relationship of the clinical event to any particular study procedure.

Not related: The temporal relationship of the clinical event to IP administration makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Related: The temporal relationship of the clinical event to study IP administration makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with information already known about the IP, and is not listed in the current IB. The IB provides further detail on signs or symptoms that might be expected with the use of the IP, including information relating to device malfunction or misuse.

8.3 Reporting and Follow-Up of Serious Adverse Events

Any SAEs reported or observed during the study whether or not attributable to the IP, or to any study procedures, or any SAE related to the product and spontaneously reported after the safety follow-up must be reported by the Principal Investigator or designee **within 24 hours after first awareness by any party involved in the study** to [redacted] and to the Sponsor.

An SAE report form must be faxed or e-mailed as an attachment to:

[redacted]	**Fax number:**	[redacted]
	E-mail:	[redacted]
	Address:	[redacted]
Sponsor Contact:	**Phone:**	[redacted]
[redacted] MD Medical Safety Officer		
	E-mail 1:	[redacted]@pmi.com
	E-mail 2:	[redacted]@pmi.com

The PI(s) or designee(s) is (are) responsible for local reporting (*e.g.*, to the IRB) of SAEs that occur during the study, according to local regulations.

Any SAE will be reported by the Sponsor to the FDA Center for Tobacco Products Office of Science within 15 business days after the report is received by the Sponsor.

Any additional/follow-up information that becomes available after the initial SAE report form has been completed will be forwarded to [redacted] and the Sponsor within 24 hours after first awareness by any person at the site using a follow-up to the existing SAE report form.

The follow-up SAE report form must include the minimum information required as described in the safety management plan (SMP) for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

All SAEs will be followed up by the PI(s) or designee(s) and/or [redacted] until their resolution or until the PI(s) or designee(s) consider(s) the event to be stabilized (*i.e.*, no

worsening of condition), or an acceptable explanation has been found (*e.g.*, a chronic condition).

The SAE report form to be used in this study is provided as a separate document and included in the Investigator site file. All SAEs will be recorded, in addition to the SAE report form.

8.4 Reporting of Other Events Critical to Safety Evaluations

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the PI(s) or designee(s) and assessed for clinical relevance. If the subject is enrolled in the extension study and, if the abnormal laboratory result is detected after signature of the extension study ICF at V10 onwards, and is considered clinically relevant (see below), this should be recorded as an AE in the CRF of the extension study. If the subject is not enrolled (e.g. screen failure), the AE should be recorded in the CRF of the original study.

The grading scheme described in the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] version 4.03 (Appendix 5) will be used by the PI(s) or designee(s) to assess abnormal laboratory AEs as follows:

- All Grade 1 abnormal laboratory values will be evaluated by the PI(s) or designee(s) with respect to Baseline value (V3 of the original study) and clinical relevance. If considered to be clinically relevant the Investigator or designee must report it as an AE. All Grade 2 and higher abnormal laboratory values must be reported as, or linked to, an AE/concomitant disease.
- If there is any worsening in grade from Grade 2 and above during the study the PI(s) or designee(s) must report this worsening as an AE.
- Where there is no grading available, the abnormal laboratory value will be evaluated by the PI(s) or designee(s) and assessed for clinical relevance. If considered to be clinically relevant, the PI(s) or designee(s) will report it as an AE.
- Any other abnormal clinical laboratory result (including those that are not part of the core safety assessments) can, at the discretion of the PI(s) or designee(s), be reviewed and assessed. Even if they do not meet the criteria of the CTCAE grading scheme (please see above), the PI(s) or designee(s) may consider them to be of clinical relevance and, if they are, must report them as AEs.
- In general, laboratory values will be recorded as ‘increased <lab parameter>’ or ‘decreased <lab parameter>’ to ensure consistency of recording/coding.

All other information (*e.g.*, relationship to IP, intensity, seriousness, outcome) will be assessed as for other AEs.

8.5 Reporting and Follow-Up of Pregnancies

For pregnancies detected at V10, subject will not be offered to enter in the extension study. A pregnancy form will be filled during V10 as part of the original study assessments. The diagnosed pregnancy will be captured in the CRF of the original study only, and not in the CRF of the extension study, as it will be considered as an event from the original study.

Any pregnancy having occurred after enrollment in the extension study, potentially associated with exposure the IP, including pregnancies spontaneously reported to the PI(s) or designee(s) after the EOS must be reported by the PI(s) or designee(s) and followed up until the pregnancy outcome is reached. Potentially associated with exposure to the IP is defined as the pregnancy where a conception date being calculated as the date after first exposure and before the last exposure to the IP. In case the conception occurs before the enrollment in the extension study but the pregnancy test is negative at V10, the occurrence of the pregnancy will be captured in the CRF of the extension study only once the pregnancy is diagnosed.

The PI(s) or designee(s) will complete a pregnancy form (provided as a separate document) for all pregnancies diagnosed after enrollment in the extension study (including positive urine pregnancy tests).

The procedure to report a pregnancy and provide any additional/follow-up information to [redacted] and the Sponsor must be followed in the same manner and within the same timelines as described for an SAE (section 8.3). No invasive study procedures, including drawing of blood must be done in such subjects after the discovery of pregnancy.

[redacted] will follow up pregnancies until an outcome is reached (*e.g.* normal delivery, spontaneous abortion or voluntary termination). Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded.

The PI(s) or designee(s) is(are) responsible for informing the IRB of any pregnancy that occurs during the study and its outcome, according to local regulations.

8.6 Adverse Events Leading to Discontinuation

Enrolled subjects who are discontinued from the extension study because of an AE will undergo early termination procedures (section 9.4) within 5 days after the day of discontinuation and enter the safety follow-up period of the extension study. The PI(s) or designee(s) will follow-up these AEs until they have been resolved, stabilized (*i.e.*, no worsening of condition), or until an acceptable explanation has been found. All ongoing AEs at the end of the study will be managed as described in section 8.2.2.1.

8.7 Investigational Device Misuse

Any occurrence of THS Tobacco Stick Holder or THS Charger misuse (use not in accordance with its label and instruction) by a subject will be documented by the PI(s) or designee(s) using a device issue log.

Investigational device misuse may result in use-related hazards.

Use-related hazards are derived from the US Food and Drug Administration Medical Device Use - Safety Guidance [39]:

- Hazards caused specifically by how a device is used.
- Unanticipated use scenarios (*e.g.*, modification of charging unit, applying any chemicals, using CCs, mechanical damage of the unit, etc.) that result in hazards must be documented and reported by the PI(s) or designee(s).

8.8 Investigational Device Malfunction

Any occurrences of malfunction of the THS Tobacco Stick Holder or THS Charger will be documented by the PI(s) or designee(s) using a device issue log.

Furthermore, any malfunctions of the THS Tobacco Stick Holder or THS Charger that lead to an AE/SAE will follow the same processes as described above.

9 STUDY ACTIVITIES

A detailed schedule of assessment can be found in Appendix 1. All assessments of the extension study will be performed in the same standardized way as in the original study to ensure homogeneity of data collection. Measurements not conducted at the exact time point, but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given time point.

In general, if no start time for a procedure is provided, then the procedure can be performed at any time during the day.

9.1 Visit 10

V10 corresponds to the last visit of the original study. For subjects willing to participate in the extension study, it also corresponds to the first visit in the extension study. Once all V10 assessments from the original study have been performed, subjects will be offered to enter into the extension study. After subjects give their written informed consent, screening procedures of the extension study can be performed. If eligibility criteria of the extension study are met subjects will be enrolled. All assessments done at V10 in the context of the original study do not need to be repeated for the extension study. The assessments done as part of the original study at V10 are given in Appendix 1.

Table 4 shows the extension study assessments that will be performed during V10.

Table 4 Time Schedule - V10 (Week 26)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Visit 10**	
At the end of V10		Subject will be offered to enter into the extension study	After all V10 assessments of the original study have been performed according to Appendix 1. Only if female subject have a negative pregnant test
During Screening		Informed consent form for extension study participation and two additional informed consent forms for biobanking	
During screening		Readiness to comply to extension study procedures (*e.g.*, willingness to use THS 2.2 for an additional 26 weeks)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Visit 10**	
During screening		Inclusion/exclusion criteria check for the enrollment into the extension study	
During the visit		AE/SAE questioning; Concomitant medication	At any time during the day
End of screening		Enrollment into the extension study after all V10 procedures completed	If all eligibility criteria are met
After enrollment		Enrolled subjects are informed to continue in their assigned study arm (THS 2.2 or CC)	
After enrollment		THS Tobacco sticks are distributed to subjects in THS 2.2 arm	
After enrollment		Check-out from site / beginning of extended exposure period	

Abbreviations:
AE = Adverse event; CC = Conventional cigarette(s); SAE = Serious adverse event; THS = Tobacco Heating System.

The sequence of assessments/events is given just for illustrative purposes. The sequence will be at the discretion of the site after signature of the ICF. If the inclusion and exclusion criteria are met, the subject will be enrolled into the extension study. However, enrollment can only take place at V10.

9.2 Extended Exposure Period

Table 5 shows the assessments that will be performed at V11, V12, V13, V14, and V15:

Table 5 Time Schedule – V11 (Week 30), V12 (Week 35), V13 (Week 39), V14 (Week 43), V15 (Week 48)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V11, V12, V13, V14, and V15**	
Start of the visit		Check-in at site	Product use will be allowed on site in the THS 2.2 and CC arms

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V11, V12, V13, V14, and V15**	
			The use of THS 2.2 in subjects randomized to CC will be forbidden
During the visit		Return of unused and partially used packs of THS Tobacco Sticks by the subject randomized to THS 2.2 arm	
During the visit		Urine pregnancy test (females only)	
During the visit		AE/SAE questioning; Concomitant medication	At any time during the day
During the visit		Weight and calculation of BMI	At V13 only
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position At any time during the day
During the visit		Information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2	
During the visit		Dispensing of THS 2.2	THS 2.2 arm only
During the visit		Distribution of the 24-hour urine containers	At V15 only
End of the visit		Check-out from site	

Abbreviations:

AE = Adverse event; CC = Conventional cigarette(s); SAE = Serious adverse event; THS = Tobacco Heating System.

Table 6 shows the assessments that will be performed at V16:

Table 6 Time Schedule - V16 (Week 52)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V16**	
Start of the visit		Check-in at site	Product use will be allowed on site in the THS 2.2 and CC arms The use of THS 2.2 in smokers randomized to CC will be forbidden
Prior to breakfast		Receipt of the subject's containers filled with 24-hour urine	The urine is collected for 24-hours ±1 hour. The start of urine collection is at subject's home the day before the visit and the end is in the morning of the visit
Prior to breakfast		Urine pregnancy test (females only)	
Prior to breakfast	√	Clinical laboratory parameters* (hematology, clinical chemistry)	Has to be done after at least 10 hours of fasting * WBC from safety will be also evaluated as part of the "smokers' health profile"
Prior to breakfast	√	Clinical risk endpoints: HDL-C, LDL-C, sICAM-1, Apo A1, Apo B, MPO, homocysteine, hsCRP, HbA1c, fibrinogen	Has to be done after at least 10 hours of fasting
Prior to breakfast	√	Blood sampling for biobanking for transcriptomics and lipidomics	If consent is obtained Has to be done after at least 10 hours of fasting
Prior to breakfast	√	Biobanking for BoExp/clinical risk endpoints in serum/plasma	If consent is obtained Has to be done after at least 10 hours of fasting
During the visit		Breakfast	
During the visit		Urine sampling to be taken from the 24-hour urine V16 container as appropriate	BoExp (all BoExp and Neq), and creatinine, in 24-hour urine Clinical risk endpoints: 11-DTX-B_2, 8 epi-$PGF_{2\alpha}$, albumin

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V16**	
			Biobanking for BoExp/clinical risk endpoints (if additional consent is obtained)
During the visit		AE/SAE questioning; concomitant medication	At any time during the day
During the visit		Physical examination	
During the visit		Lung function: • spirometry pre-salbutamol first, • lung volume using helium dilution technique pre-salbutamol, then, • spirometry post-salbutamol	Has to be done at least after 1 hour without smoking or using THS 2.2 Subject at rest for at least 15 minutes prior to lung function testing In sitting position All post-salbutamol spirometry testing will be performed 15-30 minutes post administration of salbutamol For an individual subject, the start of his/her spirometry should be organized within the time window of +/- 2 hours respective to the time of his/her spirometry tests that was performed at V3 Baseline.
During the visit	√	Nicotine and Cotinine in plasma	Irrespective of cc use
During the visit		CO breath test	Has to be done in conjunction with COHb blood sampling Irrespective of product use.
During the visit	√	COHb in blood	Has to be done in conjunction with CO breath test Irrespective of product use
During the visit		Lunch	
During the visit		Urine safety analysis	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V16**	
During the visit		Weight, calculation of BMI, and waist circumference	Weight and waist circumference to be evaluated also as clinical risk endpoints
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position At any time during the day Systolic and diastolic blood pressure to be evaluated also as clinical risk endpoints.
During the visit		ECG	After resting for at least 5 minutes in supine position prior to recording
During the visit		MCEQ questionnaire	
During the visit		Assessment of cough (VAS)	
During the visit		ITUQ questionnaire THS 2.2	THS 2.2 arm only
During the visit		Information on the risk of smoking/smoking cessation advice and debriefing on THS 2.2	
During the visit		FTND	
During the visit		Return of eDiary to the site staff	
In the morning		Return of THS 2.2 in addition to the unused and partially used packs of THS Tobacco Sticks by the subject randomized to THS 2.2	
At the end of the visit		Check-out from the site / beginning of follow up safety period	

Abbreviations:

8-epi-$PGF_{2\alpha}$ = 8-epi-prostaglandine F2α; 11-DTX-B_2 = 11-dehydro-thromboxane B2; AE = Adverse event; Apolipoprotein A1= Apo A1; Apolipoprotein B = Apo B; BMI = Body mass index; BoExp = Biomarkers of exposure; CC = Conventional cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; ECG = Electrocardiogram; FTND = Fagerström test

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		V16	

for nicotine dependence; HbA1c = Hemoglobin glycosylated A1c; HDL-C = High density lipoprotein; hs-CRP = high sensitivity C-reactive protein; ITUQ = Intent-to-use questionnaire LDL-C = Low density lipoprotein; MCEQ = Modified cigarette evaluation questionnaire; MPO = Myeloperoxidase; Neq = nicotine equivalents; SAE = Serious adverse event; sICAM-1 = soluble intercellular adhesion molecule; THS = Tobacco Heating System; WBC = White blood cell count.

9.3 Safety Follow-up Period

After V16, subject will enter the 28 day safety follow-up period of the extension study. If a subject discontinues from the study prior to V16, he/she will also enter the 28 day safety follow-up period at the time of discontinuation unless he/she is lost to follow-up.

During the 28 day safety follow-up period, there will be spontaneous reporting by the subject of new AEs and new SAEs. Any ongoing AEs/SAEs will be actively followed-up by the site.

Any AEs or SAEs that are ongoing at the end of the 28 day safety follow-up period will be managed as described in section 8.

9.4 Early Termination Procedures

The following early termination procedures will be performed within 5 days of the date of study discontinuation, if a subject is discontinued from the study:

- AE/SAE recording.
- Clinical laboratory parameters (hematology, clinical chemistry, and urine safety analysis).
- Physical examination.
- Lung function (spirometry pre-bronchodilator and spirometry post-bronchodilator). In case the value of the test(s) do not meet the criteria the subject will need to come back within a 7 day window to repeat the test(s).
- Urine pregnancy.
- Vital signs.
- ECG.
- Information on the risk of smoking, smoking cessation advice, and debriefing on THS 2.2.

If the early termination visit occurs on the same day than a planned visit (e.g. the subject wants to withdraw or is discontinued in the middle of V12), all assessments that have been performed during the planned visit should not be conducted again for the ET procedures. In case an early

termination visit is not performed, the subject will still enter into the 28 days Safety Follow-up Period after the discontinuation date.

10 CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

The Clinical Research Associate ("Monitor") of the contract research organization (CRO) will be responsible for the monitoring of the study. Monitoring will be performed according to CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

The PI(s) or designee(s) shall permit the Monitor to review study data as frequently as considered necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory met.

The PI(s) or designee(s) shall access medical records for the Monitor in order that entries in the CRFs may be verified. As part of his/her(their) responsibilities, the PI(s) or designee(s) is(are) expected to ensure that the study adheres to GCP requirements [2].

An Investigator's meeting will be held prior to the site initiation visit. During this meeting, the general training of the study procedures and specific training on selected procedures will be completed and documented.

Subsequent to the Investigator's meeting, and before the first subject is screened into the study, the site initiation visit will be conducted by the Monitor and, if necessary, together with the Sponsor or its authorized representative. The purpose of the site initiation visit is described in the monitoring plan.

During the study, the Monitor will have regular contact with the study site, including interim monitoring visits. The purpose of these visits is described in the monitoring plan.

Communication by telephone, mail, and e-mail may be used as needed to supplement site visits. The Principal Investigator and study personnel will cooperate with the Monitor, provide all appropriate documentation, and will be available to discuss the study.

The Monitor and the Sponsor's personnel will be available between visits should the Principal Investigator or other staff at the sites need information and advice.

Site visits will be made at regular intervals during the study. The frequency of the monitoring visits will be defined in the monitoring plan agreed with the Sponsor.

The PI(s) or designee(s), must be available during the monitoring visit to review the data, resolve any queries and to allow direct access to the subject's records for source data verification.

10.2 Training of Staff

A formal meeting (Investigator's meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training to the relevant

systems and other study-specific procedures. The activities of this meeting will be described in the monitoring plan.

Further to the Investigator meeting, the PI(s) or designee(s) will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the staff involved. The PI(s) or designee(s) will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

Good Clinical Practice regulations require that there are independent inspections of clinical program activities. Such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines [2], and any applicable regulatory requirements. The PI(s) or designee(s) will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.

The PI(s) or designee(s) is(are) responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the PI(s) or designee(s) understand(s) and agree(s) to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All data management activities will be described in detail in the data management plan (DMP) and documents specified therein. The electronic systems used to collect subject data, CRF and electronic patient reported outcome (ePRO), will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

Data from the extension study will be collected in a new CRF separate from the CRF of the original study. The CRF of the extension study will contain some data collected during the original study, which will be integrated from the CRF of the original study into the CRF of the extension study (e.g. medical history, ongoing concomitant medications, ongoing AEs, etc.). Subjects in the extension study will have the same identification number used during the original study.

With the exception of subject-reported outcome data, all results from the clinical assessments will be recorded in the source documents by the PI(s) or designee(s) and then captured in the CRFs at the study site. The subject questionnaires, the cough-VAS and the product use diary (tobacco and nicotine containing products) will be entered by the subject directly in an electronic diary or on paper copy. Trained study personnel will be responsible for capturing the data from the observations, tests and assessments specified in the protocol in the source documents, and then for transferring the data into the CRF according to the CRF Completion Guidelines.

The Principal Investigator(s) has(have) ultimate responsibility for the collection and reporting of all data related to the clinical study and for ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF must be electronically signed by the PI(s) to attest that the data are true and accurate. Any corrections made to source documents and/or CRFs must be clearly recorded, without obscuring the original values and must be accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject will be checked against the source documents at the study site by the Monitor. Instances of missing or unclear data will be discussed with the Investigator for resolution. For the electronic diary, all subject reported outcome data will be provided in English and Spanish and instructions will be provided in the subject's local language. A CRF will be generated for all subjects who have signed the ICF of the extension study. Every subject who signed the ICF of the extension study at V10 will be attributed the same number as in the original study.

11.1.2 Protocol Deviations

Protocol deviations are defined as deviations from the study procedures as defined in this document, including but not limited to, as 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 components of the "smokers' health profile".

All protocol deviations will be documented into the clinical trial management system (CTMS) or other approved format following site monitoring and other manual review.

Information from the source documents will represent the primary source of protocol deviations. Information following site monitoring and other manual reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in the CTMS or other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, documented and tracked as protocol deviations, as necessary.

The protocol deviations from the CTMS (or other approved format) will be reviewed against the individual data points in the CRF database. The overall procedure for managing protocol deviations is described in the SOPs and/or documented in the DMP.

11.1.3 Data Handling

All study data will be managed by the data management team at the CRO responsible for this study. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO data management team. The data management team at the CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the start of data entry. This document will describe, in details, the data management-related procedures and processes.

Data of all subjects who sign the ICF, including screening failures will be captured in the source documents. All AEs will be entered in the study database (CRF).

All data collected during the study is declared property of the Sponsor, irrespective of the location of the database and the data management CRO.

Additional details are covered in the DMP.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis are given in a SAP. Any changes to the planned statistical methods will be documented in the clinical study report. The statistical evaluation will be performed using SAS®, version 9.2 or later.

For analysis purposes, data collected in this study will be pooled with relevant data from the original study as indicated in the following sections, with reference to Baseline and data collected during visits V1 to V10.

12.1.1 Stratification Criteria

For the primary analysis of the endpoints in the "smokers' health profile", the following stratification criteria will be used:

1. Sex (male; female).
2. Site.

12.1.2 Definitions for Statistical Data Analysis

Baseline:

In general, Baseline value will be the last assessment at or prior to the V3.

Adherence to product allocation:

Adherence to THS 2.2 is defined as at least 70% THS 2.2 use, with no more than 5 CC during each single day of the randomized exposure period of the main study. The same criteria will be adopted for the extended 6-month period. Subjects in the CC arm will be considered adherent to the randomized product. For both the THS 2.2 and CC arm, any subjects reporting to having quit using tobacco-containing products (e.g. THS 2.2 and CC) will be considered not adherent to the study product allocated. Product adherence will be used for the definition of the per-protocol (PP) population (section 12.4.4).

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by product arm, product use pattern category (section 12.4.2), subject, and study visit, unless otherwise specified.

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, and number; for log-normal data the geometric mean and geometric CV will also be presented. For categorical data, frequency

counts and percentages will be presented. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

12.1.4 Handling of Missing Values and of Values Outside the Detection Limits

For 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 value below LLOQ or above ULOQ will be reported in the summaries, together with minimum and maximum of the observed values.

For daily product use data:

- Only available data will be included in the product use summaries.
- For product use categorization purposes, missing product use data will be interpolated using a moving average centered on the missing data. If more than one third of the product use data is still missing after this imputation process, the product use category will be set to missing.
- Only available product use data collected since the first day after randomization (Day 2) up until V16 (Day 16 excluded) will be considered, with the exclusion of inconsistent records and outliers. Further details will be provided in the SAP.
- If the number of subjects classified as Missing product use category is greater than 10% of the total FAS-EX population, a sensitivity analysis will be produced for the FAS-EX, by reanalysing the primary endpoints re-classifying all subjects based on the available data in the diary.

For MCEQ questionnaire data, total scores and domain or subscale scores will be derived by averaging the individual non-missing item scores if at least 50% are non-missing, otherwise they will be set to missing.

The FTND total score will be derived by summing the individual item scores if all items are non-missing; if any items are missing the total score will be set to missing.

Further details are provided in the SAP.

12.1.5 Significance Level for Inferential Analysis

This study has no formal pre-specified hypotheses associated with the study objectives. Estimates of THS 2.2 effect will be presented However, 95% CI will accompany all effect estimates, with no multiplicity adjustment.

12.2 Determination of Sample Size and Power Consideration

The sample size for this study was defined based on the sample size requirements of the original study, for which the sample size was calculated to ensure an overall study power of at least 90%, while maintaining at least 80% power to detect the expected effect of THS 2.2 as compared to CC for each individual endpoint of the "smokers' health profile", over 26 weeks of exposure. This required 475 subjects randomized per group accounting for an anticipated 75% of the THS 2.2 arm to be Mostly THS 2.2 users (i.e. report at least 70% THS 2.2 use).

Based on the assumptions that 30% of the 950 subjects will not be enrolled or will drop out from the extension study and a potential decrease from 75% to 50% of Mostly THS 2.2 users among subjects randomized to THS 2.2, the study will have at least 90% probability to determine the effect of THS 2.2 as compared to CC on FEV1 at V16 with a margin of error (95% CI) of at most ±1.5 %pred. The anticipated SD of 6.4 %pred was estimated using the results of the "Lung Health Study" [1].

Following our current understanding of product use data in the main study, the definition of the product use categories was redefined and the underlying assumptions re-evaluated so that approximately 60% of the subjects in the THS 2.2 arm are expected to be in the THS-use category, with an anticipated 20% of subjects drop-out or reporting insufficient product use data in the two arms of the main study. Based on the 65% rate of enrollment into the extension study observed among subjects randomized in the main study, the extension study will have more than 90% probability to determine the effect of THS-use compared to CC-use on FEV1 at V16 with a margin of error (95% CI) of at most ±1.5 %pred.

12.3 Product Use

Although subjects are being requested to use solely the product allocated to their respective study arm, it is considered that not all subjects that were randomized to the THS 2.2 arm in the original study will exclusively use THS 2.2 at all times during the study. Subjects may concomitantly use THS 2.2 and CC (dual-use). To assess dual use of THS 2.2 and CC, PMI has defined categories of pattern of product use.

Product use pattern categories within an analysis period will be calculated based on the percentage of product use that is THS 2.2 product use of the overall product use, including THS Tobacco Sticks and conventional cigarettes (CC). During each analysis period, the percentage of THS 2.2 product use will be calculated as:

$$= 100 \times \frac{Number\ of\ THS\ Tobacco\ Sticks}{Number\ of\ THS\ Tobacco\ Sticks + Number\ of\ CC}$$

General product use pattern categories are defined as in Table 7. General product use categories will be used for both safety summaries and non-safety analysis. More granular product exposure categories will be used for the detailed description of the product use patterns observed in the study. Full details of the product use categories derivation are reported in the SAP.

Table 7: Actual Product Use General Pattern Categories

Category Label	General Description
THS-use	• ≥ 1 THSts or CC and • ≥ 70% THSts use in the analysis period and • ≥ 70% THSts use on ≥ 50% of the days in the analysis period
Dual-use	• ≥ 1 THSts or CC and • 1% ≤ THSts < 70% in the analysis period or • THS-use and CC-use don't apply due to < 50% of the days
CC-use	• ≥ 1 THSts or CC and • < 1% THSts in the analysis period and • < 1% THSts on ≥ 50% of the days in analysis period
Other-use	General category encompassing subjects with missing product use, or subjects using e-cigarettes or other tobacco products, subjects who quit, or subjects who switched across different use patterns between consecutive analysis periods.

Rules applied over 6-mont analysis periods. Details of combined 12-month the product use categories are reported in the SAP. THSts = THS Tobacco Stick; THS=Tobacco Heating System; CC= Conventional Cigarette.

12.4 Analysis Population

The Full Analysis Set – as Exposed (FAS-EX) will be the primary analysis set for clinical risk endpoints, BoExp, and questionnaires, based on the overall product use pattern categories.

Supportive analyses will be run on the per-protocol (PP) population and a sensitivity analysis will be conducted on the Full Analysis Set – as Randomized (FAS-AR).

The primary population for the assessment of safety will be the safety population. Safety will be summarized and presented by randomization arm and according to product use pattern categories.

12.4.1 Full Analysis Set - as Randomized (FAS-AR)

The FAS-AR consists of all the randomized subjects with signed ICF who have both a valid baseline and at least one valid post-randomization value for one of the primary endpoints.

Subjects enrolled at sites that are terminated due to findings of non-compliance with GCP and/or with the protocol will be excluded from the FAS-AR.

Subjects included in the FAS-AR are analyzed as per randomized arm.

12.4.2 Full Analysis Set - as Exposed (FAS-EX)

The FAS-EX consists of all subjects in FAS-AR who have at least one record of reported product use diary post randomization.

The exposure assignment for the FAS-EX will be actual product exposure, as defined by the product use pattern categories estimated during the 12 month period]V4, V16[. The product use pattern categories are defined in section 12.3.

12.4.3 Per-Protocol Population

The PP population is a subset of FAS-EX and includes all subjects who:

- Have a product use pattern category THS-use if randomized to THS 2.2 or have product use pattern category CC-use if randomized to CC.
- Were included in the PP population in the original study.
- Do not make a quit attempt.
- Have no major protocol deviations that impact the overall subject evaluability (as detailed in the SAP).
- Have data for at least one endpoint of the “smoker’s health profile” which is not missing or excluded from the PP analysis at V7, V10, or V16, because of a major protocol deviation impacting evaluability.

12.4.4 Safety Population

The safety population consists of all the subjects enrolled with signed ICF who have at least one valid value for a safety assessment. This analysis set excludes all subjects enrolled in sites terminated due to findings of non-compliance with GCP and/or with the protocol. In general, the exposure assignment for the full safety population will be by randomization arm and according to product use pattern categories as defined in section 12.3.

12.5 Primary Analysis

12.5.1 Primary Endpoint Analysis Variables

The "smokers' health profile" endpoints to be analyzed at V16 are:

- HDL-C.
- WBC.
- sICAM-1.
- 11-DTX-B_2.
- 8-epi-$PGF_{2\alpha}$.
- COHb.
- FEV_1.
- Total NNAL.

See section 3.1.

Study Hypothesis:

No hypotheses are to be tested. The objective of the study is to determine the effect of THS 2.2 compared to CC at week 52 on the components of the "smokers' health profile" and to provide additional information to the results of the original study (ZRHR-ERS-09-US) for a prolonged exposure period.

Exploratory statistical hypothesis testing will be conducted to assess baseline comparability (see Section 12.5.2 "Baseline Comparability") and to evaluate the THS 2.2 effect on selected endpoints (as detailed in the SAP). All the THS 2.2 effect estimates will be accompanied by 95% CI.

Evaluation Criterion:

The study will target to describe the 95% confidence intervals (CI) of the THS 2.2 effect as compared to CC at week 52 on the components of the "smokers' health profile" estimated with a precision of ±75% of the anticipated THS 2.2 effect at week 52.

12.5.2 Baseline Comparability

There will be no formal comparison of Baseline data, however exploratory statistical hypothesis testing will be conducted to assess the characteristics of the subjects enrolling in the extension study. Baseline comparability will be assessed between subjects enrolled and not enrolled in the study among subjects who completed V10, by means of analysis of variance method and chi-square tests for continuous and categorical variables, respectively.

12.5.3 Descriptive Analysis

Primary endpoints will be summarized at Baseline, V7, V10 and at V16 for the product use categories at V16 of FAS-EX, and by randomization arm for the FAS-AR and PP population.

12.5.4 Confirmatory Analysis

No formal confirmatory analysis is foreseen in this study.

FEV_1, HDL-C, and WBC will be analyzed in the real scale. Other clinical risk endpoints, which will be analyzed in the logarithmic scale, will be back-transformed to provide relative effects.

The primary analysis for the "smokers' health profile" endpoints will be based on a mixed model for repeated measurements (MMRM). The model will include the endpoint value as the dependent variable, product use pattern category, visit (V7, V10, and V16), and exposure by visit interaction as fixed effects, with adjustment for site, sex, and Baseline endpoint value. In order to adjust for potential residual confounding, covariates found to be not balanced between THS-use and CC-use will be included in the final model. 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).

The point and interval estimate of the contrast of THS-use versus CC-use at V16 will be tabulated for the FAS-EX.

Supportive analysis will be conducted on the FAS-AR and PP set.

The detailed analysis methods, including subgroup analyses, are given in the SAP.

12.6 Secondary Analysis

12.6.1 Secondary Endpoint Analysis Variables

See section 3.2.

The details on derivation rules are provided in the SAP.

12.6.2 Descriptive Analysis

The number of CC or THS Tobacco Sticks used daily (as reported on the self-reported product use electronic diary) will be described over time on FAS-AR, FAS-EX, and on the safety population.

The levels of the BoExp and nicotine exposure level and their percent change from Baseline will be listed and summarized over the 12-month study period for the FAS-AR, FAS-EX and PP population.

The levels of lung function and CVD clinical risk endpoints will be summarized for the FAS-EX over the 12-month study period, along with change from baseline.

A supportive analysis will be conducted on the "smokers' health profile" endpoints for the FAS-EX, FAS-AR, and PP population to compare the THS-use versus CC-use, and Dual-use versus CC-use at V16 by means of the MMRM approach used for the primary analysis. The estimates of the difference/percent reduction (and 2-sided p-values) will be presented together with 95% CI for THS-use versus CC-use and Dual-use vs CC-use. The same approach will be adopted for the analysis of BoExp, lung function, and CVD risk endpoints.

The number and percentage of subjects reporting a cough will be summarized for FAS-EX over the 12-month study period. A logistic regression model will be used to evaluate the differences between incidence rates (with 2-sided p-values) and 95% CI for the need to cough between THS-use and CC-use at V16. The models will only include terms for visit, baseline level and its interaction with visit, sex, Caucasian origin, and product use pattern category and its interaction with visit. The point and 95% CI of LS means of the incidence rates and their difference (with 2-sided p-values) will also be produced for Dual-use versus CC-use. The responses to the individual items, including the VAS score and change from Baseline, and 3 Likert scales measuring the intensity and frequency of cough, and the amount of sputum production will be listed and summarized for all subjects who filled in the questionnaire.

The change from Baseline will be calculated for the five domain scores of the MCEQ for the FAS-AR, FAS-EX and PP population over the 12-month study period. Scores and changes from baseline will be listed and summarized.

The FTND score and the number and percent of subjects in each category of the FTND score and of the response to the first item of the FTND will be summarized for FAS-EX and PP population

during the 12-month period The change from V1 in the FTND score category and for response to the first item of the FTND will be presented in a shift table.

The number and proportion of subject responses to items of the ITUQ will be summarized. Changes in response categories will also be summarized in shift tables by product use pattern groups for FAS-EX and PP during the 12-month period.

The distribution of dual use will be summarized by cross-tabulation of the frequency (number and percent) of subjects for the categories of the following two variables for the FAS-EX population: average number of CC smoked over a 6 month period and the average number of THS Tobacco Sticks used over a 6 month period. To describe the effect of dual use on the components of the "smokers' health profile" the exposure-response relationship between the CC and THS 2.2 exposure and the "smokers' health profile" endpoints level is evaluated by means of the following approach based on method proposed by Follmann [40]. The details on the analysis method are described in the SAP.

12.6.3 Inferential Analysis

See section 12.1.5.

12.6.4 Safety Analysis

All safety data collected during the study will be provided in listings by randomization arm, site, subject and product use pattern category defined over the 12-month period. Safety study periods are defined as follows:

- Screening: [Screening to V3]
- Product Trial:]V3 to V4]
- Exposure:]V4 to V16]
- Safety Follow-up: [Start to End of Safety Follow-up]

Summaries of safety parameters will be conducted on the safety population. Unless otherwise specified, summaries will be produced by randomization arm and product use pattern categories over the relevant safety exposure periods.

Adverse event data will serve as the primary assessment of safety. Other safety variables monitored in this study include: respiratory symptoms (cough assessment VAS and Likert scales); vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); electrocardiogram (ECG) data; clinical chemistry, hematology, concomitant medications, and urine analysis safety panel; physical examination.

The number and percentage of subjects with AEs and SAEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA), system organ class (SOC) and preferred term (PT) for the safety population overall, and in analysis time intervals. Summaries will also be presented for AEs leading to withdrawal, AEs leading to death, AEs by relatedness to product

exposure and AEs by severity. Tabulations will be performed for both the number of subjects experiencing an event and the number of events for the Safety population.

The number and percentage of subjects with clinical findings will be summarized for the safety population. Shift tables showing change from Baseline of clinical findings will be provided for: ECGs, COPD categories, and laboratory parameters (both shifts in normal ranges and toxicity grades). Descriptive statistics will be summarized by visit and change from Baseline for laboratory parameters, physical examination, ECG, respiratory symptoms, and vital signs.

12.7 Exploratory Analysis

12.7.1 Exploratory Endpoint Analysis Variables

Not applicable.

12.7.2 Descriptive Analysis

Not applicable.

12.8 Demographics and Baseline Characteristics

The demographic variables age, sex, race, body weight, height, BMI and waist circumference will be summarized by product use pattern categories and by sex for the FAS-EX. Other baseline characteristics including scores for SES questionnaire, smoking history, and subjects' answer to product preference will also be included in the table.

Demographic and other baseline characteristics will also be summarized for the FAS-AR, safety and PP population. All data will be listed by randomization arms.

No inferential analyses will be presented for the demographic and baseline characteristics.

12.9 Interim Analysis

There are no planned interim analyses.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Study Administrative Structure

13.1.1 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland Phone: + 41 (0) 58 242 2111 Fax: + 41 (0) 58 242 2811
[redacted] Clinical Scientist	Phone: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted], PhD Study Statistician	Phone: +41[redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted], MD Medical Safety Officer	Phone: +41 [redacted] E-mail 1: [redacted]@pmi.com E-mail 2: [redacted]@pmi.com
[redacted], PhD Clinical Study Manager	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com

13.1.2 Other Responsibilities

All duties and responsibilities transferred to Covance by PMI will be defined in the agreement signed between the two parties.

The name of all sites is listed below:

• [redacted] Tempe, AZ 85283
• [redacted] Clearwater, FL 33765
• [redacted] Daytona Beach, FL 32117
• [redacted] Orlando, FL 32806
• [redacted] Tampa, FL 33603
• [redacted] The Villages, FL 32162
• [redacted] Lexington, KY 40509
• [redacted] Lincoln, NE 68502
• [redacted] Raleigh, NC 27609

• [redacted] Charlotte, NC 28209
• [redacted] Wilmington, NC 28401
• [redacted] Cary, NC 27518
• [redacted] Dayton, OH 45417
• [redacted] Bristol, TN 37620
• [redacted] Knoxville, TN 37920
• [redacted] San Angelo, TX 76904
• [redacted] Austin, TX 78705
• [redacted] Fort Worth, TX 76135
• [redacted]

Richmond, VA

Any SAEs or pregnancies will be handled by:

[redacted]
Switzerland
Phone: +41 [redacted]
Fax: +41 [redacted]
E-mail: [redacted]

Details of the laboratories conducting the clinical safety laboratory services, biopharmaceutical analyses and the analyses of BoExp are shown in Appendix 2.

13.2 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the subject. An agreement to disclose any such information will be obtained from the subject in writing and signed by the subject, in compliance with all local and national data protection and privacy legislation.

The anonymity of subjects participating in this study will be maintained. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their subject (or randomization) number/code, sex, and date of birth, but not by name, initial, or any other details relating to identifiable person (*e.g.*, address, social security number, medical chart number, etc.). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

The blood samples for transcriptomics and lipidomics the data related to these samples will be anonymized. Anonymized data and samples are initially single or double coded where the link between the subjects' identifiers and the unique code(s) is subsequently deleted. This is applicable for the blood biobanking for transcriptomics and lipidomics.

Any documents that allow full identification of the subject (*e.g.*, the subject's signed ICF) must be maintained in confidence by the Principal Investigator or designee. If any document relating to this study shows a subject's name or any other details relating to an identifiable person (*e.g.*, address, social security number, medical chart number, etc.), it is the responsibility of the Principal Investigator or designee to ensure that the name or other identifiable details be

obscured before a copy of that document is supplied to the Sponsor or the Sponsor's authorized representative.

13.3 Access to Source Documents

Subjects will be informed that, during as well as after the course of the clinical study, the Sponsor, any authorized representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and ensure that all personal information made available for inspection is handled in the strictest confidence and in accordance with national and local data protection and privacy legislation.

The PI(s) and all study site staff involved with the study must permit direct access to source data/documents for study related monitoring, audits, IRB review, and regulatory inspection(s).

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans, and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study, and the actions taken will be maintained by the Investigator/study site for the study, as required by ICH GCP [2] and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in Section 8 of the ICH Tripartite Guideline for Good Clinical Practice [2].

Essential documents must be retained by the Investigator for a minimum of:

- At least 15 years after completion or discontinuation of the study, or
- At least 2 years depending on, for example, the circumstances.
- After formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Signed informed consent documents for all subjects and master ICF.
- Subject identification code list, screening log, and enrollment log (if applicable).
- Record of all communications between the Investigator and the IRB, composition of the IRB.
- Record of all communications/contact between the PI(s) or designee(s), Sponsor, and its authorized representatives.

- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curricula vitae, and their signatures.
- Investigator logs.
- CRFs, study specific questionnaires (and associated data/scoring), subject diaries.
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (*e.g.*, ECGs, consultation reports, physical examination, laboratory records) or any electronically captured study source data.
- Clinical laboratory reports, laboratory normal ranges.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).
- Record of any body fluids or tissue samples collected and retained.
- Device issue log, IP accountability logs, dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

It is the responsibility of the Sponsor to inform the PI(s)/study site(s) as to when these documents no longer need to be retained.

The PI(s)/study site(s) must take measures to prevent accidental or premature destruction of these documents.

If the PI(s) wish(es) to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The PI(s) or designee(s) must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the archives of the PI(s). If a Principal Investigator is unable to meet this obligation, he/she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study as long as the IP is on the market, and/or for 15 years after the CSR has been finalized.

13.5 Clinical Study Report

The Sponsor must ensure that a CSR for this study is prepared regardless of whether the study is completed or prematurely terminated.

The CSR will be written based on standards of the ICH Guideline for the structure and content of clinical study reports [41]. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IRB will be complied with as requested by local requirements.

The results of the additional variables for analysis will be presented in reports separate from the study CSR.

13.6 Financial Disclosure

Principal Investigator(s) is (are) required to provide financial disclosure information to the Sponsor. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IRB, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice will be given to the Sponsor prior to any such disclosure.

The Sponsor plans to disclose details of the study protocol on a web-based, publicly available, clinical trial register database (*e.g.*, ClinicalTrials.gov).

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15 APPENDICES

Appendix 1 Schedule of Events

Table A1 Study Assessments

Visits / Assessments	ZRHR-ERS-09-US	ZRHR-ERS-09-EXT-US Extended Exposure Period							Safety Follow-Up [g]
	V3 (Baseline)	V10		V11	V12	V13	V14	V15	V16	28 days
		ERS	EXT							
Study week (W)	-	W26		W30	W35	W39	W43	W48	W52	
Informed consent and additional ICFs for biobanking for ZRHR-ERS-09-EXT-US			●							
Inclusion / exclusion check for ZRHR-ERS-09-US	● V1+V3									
Inclusion / exclusion check for ZRHR-ERS-09-EXT-US			●							
Readiness to comply with study procedures and to use THS 2.2 for 26 additional weeks			●							
Enrollment of ZRHR-ERS- 09-US	●									
Enrollment of ZRHR-ERS-09-EXT-US			●							
Information on the risk of smoking, advice on smoking cessation (SC), and debriefing on THS 2.2	●	●		●	●	●	●	●	●	
Concomitant medication	●	●	●	●	●	●	●	●	●	

Visits Assessments	ZRHR-ERS-09-US	ZRHR-ERS-09-EXT-US Extended Exposure Period							Safety Follow-Up [g]
	V3 (Baseline)	V10		V11	V12	V13	V14	V15	V16	28 days
		ERS	EXT							
U: Pregnancy test (females)	●	●		●	●	●	●	●	●	
B/U: Clinical chemistry, hematology, urine analysis [a]	●	●							●	
ECG		●							●	
Vital signs [b]	●	●		●	●	●	●	●	●	
Waist circumference	●	●							●	
Weight and body mass index (BMI) [c]	●	●				●			●	
Physical examination	●	●							●	
Dispensing of THS 2.2	●		●	●	●	●	●	●		
CO breath test [d]	●	●							●	
U: BoExp in urine (Table A2)	●	●							●	
U: CVD clinical risk endpoints in urine (Table A2)	●	●							●	
B: CVD clinical risk endpoints (Table A3)	●	●							●	
B: BoExp in blood (Table A3)	●	●							●	
Pre-bronchodilator spirometry testing [e]		●							●	
Post-bronchodilator spirometry testing [e]	●	●							●	
Lung volume [e]	●	●							●	

Visits Assessments	ZRHR-ERS-09-US	ZRHR-ERS-09-EXT-US Extended Exposure Period								Safety Follow-Up [g]
	V3 (Baseline)	V10		V11	V12	V13	V14	V15	V16	28 days
		ERS	EXT							
Cough questionnaire	●	●							●	
MCEQ questionnaire	●	●							●	
Product use diary (daily) [f]	●		●	●	●	●	●	●	●	
FTND		●							●	
Intent to use THS 2.2 questionnaire (ITUQ) [h]		●							●	
AE/SAE recording [i]	●	●	●	●	●	●	●	●	●	●
U: Biobanking (Table A2) [j]	●	●							●	
B: Biobanking for BoExp and clinical risk endpoints (Table A3) [j]	●	●							●	
B: Biobanking for transcriptomics and lipidomics (Table A3) [j]	●	●							●	

Abbreviations: AE = Adverse event; B: Blood sample required; BMI = Body mass index; BoExp = Biomarkers of exposure; CC = Conventional cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; CVD = Cardiovascular disease; ECG = Electrocardiogram; FTND = Fagerström test for nicotine dependence; MCEQ = Modified cigarette evaluation questionnaire; SAE = Serious adverse event; THS = Tobacco Heating System; U = Urine sample required; VAS = Visual analog scale

[a] Safety laboratory parameters will be evaluated in at least 10 hours of fasting conditions.

Hematology: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, white blood cell count, differential white blood cell count. Platelet count, white blood cell count from hematology will be evaluated as clinical risk endpoints. **Urine analysis**: pH, bilirubin, glucose, nitrite, red blood cell traces, protein, specify gravity. **Clinical chemistry**: albumin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, triglycerides. White blood cell count (WBC) will also be evaluated as part of the "smokers' health profile".

[b] Systolic and diastolic blood pressure, pulse rate, and respiratory rate. Vital signs will be assessed after at least 5 minutes in supine position.

[c] Height will be transferred from the original study

[d] CO breath test: the test will be conducted once and should be done in conjunction with COHb blood where applicable.

[e] Lung function assessments must be performed in the following sequence:

- Pre-bronchodilator spirometry testing.
- Pre-bronchodilator lung volume using helium dilution (only at V10 and V16).
- Post-bronchodilator spirometry testing.

[f] Use of any tobacco/nicotine containing products will be captured in the ediary.

[g] Early termination procedures will be conducted in subjects who terminate from the study earlier.

[h] At V16, only subjects in the THS 2.2 arm will answer to the ITUQ.

[i] During the safety follow-up period, spontaneous reporting of new AEs/SAEs by the subject will be done.

[j] Once at every visit. Samples will only be taken if additional ICF for sample biobanking is signed by the subject.

All assessments done at V10 in the context of the original study do not need to be repeated for the extension study.

Table A2 Schedule for 24-hour Urine Collection Assessments

	ZRHR-ERS-09-US			ZRHR-ERS-09-EXT-US
	V3 (Baseline)	V10		V16
		ERS	EXT	
Exposure				
BoExp in urine [a]	●	●		●
CVD Clinical Risk Endpoints				
11-DTXB$_2$, 8-epi-PGF$_{2\alpha}$, albumin	●	●		●
Others				
Creatinine	●	●		●
Biobanking for BoExp and clinical risk endpoints [b]	●	●		●

Abbreviations: BoExp = Biomarker(s) of exposure; CVD = Cardiovascular disease; 8-epi-PGF$_{2\alpha}$ = 8-epi-prostaglandine F$_{2\alpha}$; 11-DTXB$_2$ = 11-dehydrothromboxane B$_2$.

[a] 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL), total N-nitrosonornicotine (total NNN), nicotine equivalents (Neq).

[b] Samples will only be taken if additional ICF for biobanking is signed by the subject

All assessments done at V10 in the context of the original study do not need to be repeated for the extension study.

Table A3 Schedule for Blood/Serum/Plasma Assessments (Except Hematology and Clinical Chemistry)

	ZRHR-ERS-09-US			ZRHR-ERS-09-EXT-US
	V3 (Baseline)	V10		V16
		ERS	EXT	
Blood				
CVD clinical risk endpoints (COHb and HbA1c [a]	●	●		●
Biobanking [b]	●	●		●
Plasma				
CVD clinical risk endpoints (fibrinogen and homocysteine)	●	●		●
Biobanking [b]	●	●		●
BoExp: nicotine and cotinine	●	●		●
Serum				
CVD clinical risk endpoints [c]	●	●		●
Biobanking [b]	●	●		●

Abbreviations: BoExp = Biomarker(s) of exposure; CVD = Cardiovascular disease; COHb = Carboxyhemoglobin; HbA1c = Hemoglobin glycosylated A1c

[a] WBC and platelet count will be taken from the laboratory safety parameters.

[b] Samples must only be taken if additional ICF for biobanking is signed by the subject.

[c] sICAM-1, MPO, LDL-C, HDL-C, hs-CRP, Apo A1 and Apo B.

All assessments done at V10 in the context of the original study do not need to be repeated for the extension study.

Appendix 2 Concomitant Medication and Impact on Clinical Risk Endpoints (With Half-Lives)

Drug	Biological or Elimination Half-Life (h)	Last Dose Applied in Hours Prior to Lab Value Tested (5 x Half-Life)	Impact on Endpoint
Vitamins[+]			
Pyridoxine (Vitamin B6)	2 - 5	10 - 25	HDL-C
Cyanocobalamin (Vitamin B12)	approx. 24 - 48	120 - 240 (≈ 5 - 10 days)	HDL-C
Thiamine Chloride (Vitamin B1)	4 - 6	20 - 30	HDL-C
Nicotinic acid (Vitamin B3)	approx. 24	120 (≈ 5 days)	HDL-C
Ascorbic acid (Vitamin C)	2.9	14.5	HDL-C
Alpha-Tocopherol (Vitamin E)	approx. 5 - 7 days	approx. 25 - 35 days	PGF2α
Systemic and Inhaled Drugs Affecting Spirometry			
Anticholinergic/Antimuscarinic			
Ipratropiumbromide	3.6	18	FEV_1
Tiotropium	120 - 144 (≈ 5 - 6 days)	600 - 720 (≈ 25 - 30 days)	FEV_1
Aclidinium bromide	2 - 3	10 - 15	
Short-acting β-agonists, orally taken			
Terbutaline sulfate	Plasma $t_{1/2}$: 3 - 4	Plasma $t_{1/2}$: 15 - 20	FEV_1
Bambuterol	22 - 24	110 - 120 (≈ 4.6 - 5 days)	FEV_1
Inhaled short-acting β-agonists			
Salbutamol sulfate	Plasma $t_{1/2}$: 2.7 - 5	Plasma $t_{1/2}$: 13.5 - 25	FEV_1
Fenoterol	approx. 3	approx. 15	FEV_1

Drug	Biological or Elimination Half-Life (h)	Last Dose Applied in Hours Prior to Lab Value Tested (5 x Half-Life)	Impact on Endpoint
Inhaled long-acting β-agonists			
Formoterol fumarate	approx. 5	approx. 25	FEV_1
Indacaterol maleate	40 - 52	200 - 260 (≈ 8.3 - 10.8 days)	FEV_1
Salmeterol	n.a. no systemic effect	n.a	FEV_1
Inhaled Glucocorticosteroids			
Beclomethasone	2.8	14	FEV_1
Budesonide	2 - 3	10 - 15	FEV_1
Ciclesonide	6 - 7	30 - 42 (≈ 1.25 - 1.75 days)	FEV_1
Fluticasone propionate	16 - 21.3	80 - 106.5 (≈ 3.3 - 4.4 days)	FEV_1
Systemic broncholytic drugs			
Montelukast	Plasma $t_{1/2}$: 2,7 – 5,5	13.5 - 27.5	FEV_1
Aminophylline, Theophylline	7 - 9	35 - 45	FEV_1
Roflumilast	Plasma $t_{1/2}$: 17	85 (≈ 3.5 days)	FEV_1
β-blockers			
Atenolol	6 -10	30 – 50 (≈1.25 - 2 days)	FEV_1
Metoprolol	3 - 5	15 - 25	FEV_1
Bisoprolol	17 ± 5	85 (≈3.5 days)	FEV_1
Antiplatelet agents			
Phenprocoumon	165 (≈ 6.9 days)	825 (≈ 34 days)	$PGF_{2\alpha}$

Drug	Biological or Elimination Half-Life (h)	Last Dose Applied in Hours Prior to Lab Value Tested (5 x Half-Life)	Impact on Endpoint
Apixaban	12	60 (≈ 2.5 days)	$PGF_{2\alpha}$
Warfarin	Plasma $t_{1/2}$: approx. 35 - 45	175 - 225 (≈ 7.3 - 9.4 days)	$PGF_{2\alpha}$
Rivaroxaban	5 - 13 (age - dependent)	25 - 65 (≈ 1 - 2.7 days)	$PGF_{2\alpha}$
Acetylsalicylic acid	2 - 30 (dose - dependent)	10 - 150 (up to 6.25 days)	$PGF_{2\alpha}$
Antidiabetic drugs			
Acarbose	9,6 ± 4,4	48 (≈ 2 days)	11-DTX-B_2
Metformin	6.5	32.5 (≈ 1.3 days)	11-DTX-B_2
Vildagliptin	3	15	11-DTX-B_2
Saxagliptin	26.9	134.5 (≈ 5.6 days)	11-DTX-B_2
Repaglinide	4 - 6	20 - 30 (up to 1.25 days)	11-DTX-B_2
Glyburide	8 - 10	40 - 50 (≈ 1.7 - 2.1 days)	11-DTX-B_2
Glimepiride	5 - 8	20 - 40 (up to 1.7 days)	11-DTX-B_2
Pioglitazone	16 - 23	80 - 115 (≈ 3.3 - 4.8 days)	HDL-C
NSAIDs			
Celecoxib	8 - 12	40 - 60 (≈ 1.7-2.5 days)	WBC, 11-DTX-B_2
Diclofenac	approx. 2	approx. 10	WBC, 11-DTX-B_2

Drug	Biological or Elimination Half-Life (h)	Last Dose Applied in Hours Prior to Lab Value Tested (5 x Half-Life)	Impact on Endpoint
Indometacin	2; terminal phase: 4 - 11	10; terminal phase: 20-55 (up to 2.3 days)	WBC, 11-DTX-B_2
Meloxicam	approx. 20	approx. 100 (≈ 4.2 days)	WBC, 11-DTX-B_2
Piroxicam	approx. 50	250 (≈ 10.4 days)	WBC, 11-DTX-B_2
Ibuprofen	1.8 - 3.5	9 - 17.5	WBC, 11-DTX-B_2
Ketoprofen	1.5 - 2.5 (up to 8)	7.5 - 12.5 (up to 40)	WBC, 11-DTX-B_2
Naproxen	10 - 18	50 - 90 (≈ 2.1 - 3.75 days)	WBC, 11-DTX-B_2
Angiotensin-converting enzyme inhibitors			
Enalapril	at least 24	at least 120 (at least 5 days)	11-DTX-B_2
Quinapril	approx. 26	approx. 130 (≈ 5.4 days)	11-DTX-B_2
Ramipril	13 - 17	65 - 85 (≈ 2.7 - 3.5 days)	11-DTX-B_2
Lisinopril	12.6	63 (≈ 2.6 days)	11-DTX-B_2
Antidepressant Drugs			
Bupropion	20	100 (≈ 4.2 days)	WBC
Selective serotonin reuptake inhibitors (SSRIs)			
Citalopram	35	175 (≈ 7.29 days)	WBC
Escitalopram	27 – 32	135 – 160 (up to 6.67 days)	WBC

Drug	Biological or Elimination Half-Life (h)	Last Dose Applied in Hours Prior to Lab Value Tested (5 x Half-Life)	Impact on Endpoint
Fluoxetine	Initial: 24 - 72 Chronic: 96 – 144	Initial: 120 – 360 (up to 15 days) Chronic: 480 – 720 (up to 30 days)	WBC
Fluvoxamine	16	80 (≈ 3.33 days)	WBC
Paroxetine	21	105 (≈ 4.38 days)	WBC
Sertraline	26	130 (≈ 5.42 days)	WBC
Serotonin–norepinephrine reuptake inhibitors (SNRIs)			WBC
Venlafaxine	5 ± 2	25 ± 10 (≈ 1.0 ± 0.4 days)	
Tricyclic antidepressants			WBC
Tricyclic clomipramine	20 - 26	100 - 130 (≈ 4.2 - 5.4 days)	
Non-specified antidepressant drug class			WBC
Nefazodone	11 - 24	55 - 120 (≈ 2.3 - 5 days)	WBC
Lipid lowering drugs			
Fibrate			
Fenofibrate	Plasma $t_{1/2}$: approx. 20	approx. 100 (≈ 4.2 days)	HDL-C, total cholesterol (TC), triglycerides (TG)
Gemfibrozil	1.3 - 1.5	6.5 - 7.5	HDL-C, apolipoproteins
Bile acid sequestrants			
Cholestyramine	no absorption into blood stream	n.a.	HDL-C

Drug	Biological or Elimination Half-Life (h)	Last Dose Applied in Hours Prior to Lab Value Tested (5 x Half-Life)	Impact on Endpoint
Statins			
Atorvastatin	20 - 30	100 - 150 (≈ 4.2 - 6.25 days)	HDL-C, 11-DTX-B_2
Simvastatin	approx. 2-3	10 - 15	HDL-C, 11-DTX-B_2
Rosuvastatin	approx. 19	95	HDL-C, 11-DTX-B_2
Fluvastatin	2.3 ± 0.9	11.5 ± 4.5	HDL-C, 11-DTX-B_2

* n.a. = not applicable

Appendix 3 Participating Laboratories

[redacted]
[redacted]
[redacted]
[redacted] USA

USA:

[redacted]
[redacted]
[redacted] USA
Tel: [redacted]
Fax: [redacted]

Geneva:

[redacted]
[redacted]
Tel: +41 [redacted]
Fax: +41 [redacted]

[redacted] ***(USA and Switzerland)***

USA:

[redacted]
[redacted]
68502, USA

Switzerland:

[redacted]
[redacted]
Switzerland

More details will be found in the study laboratory manuals.

For biobanking of samples:

BIOSTORAGE TECHNOLOGIES

Germany:

[redacted]

Germany

USA:

[redacted]

USA

Appendix 4 Investigational Product and Instructions for Use

The product user guide was provided as a separate document during the original study.

Appendix 5 Abnormal Laboratory Values

ABNORMAL LABORATORY VALUES RATING: SERUM CHEMISTRY PARAMETERS

Serum Chemistry *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Sodium - Hyponatremia (mmol/L) [1]	< LLN - 130	-	< 130 - 120	< 120
Sodium – Hypernatremia (mmol/L) [1]	> ULN - 150	> 150 - 155	> 155 - 160 hospitalization indicated	> 160
Potassium – Hyperkalemia (mmol/L) [1]	> ULN - 5.5	> 5.5 - 6.0	> 6.0 -7.0; hospitalization indicated	> 7.0
Potassium – Hypokalemia (mmol/L) [1]	< LLN - 3.0	< LLN - 3.0; symptomatic; intervention indicated	< 3.0 - 2.5 hospitalization indicated	< 2.5
Glucose - Hypoglycemia [1] (mg/dL) (mmol/L)	< LLN - 55 < LLN - 3.0	< 55 - 40 < 3.0 - 2.2	< 40 - 30 < 2.2 - 1.7	< 30 < 1.7
Glucose - Hyperglycemia: [1] Fasting (mg/dL) (mmol/L)	> ULN - 160 > ULN - 8.9	> 160 - 250 > 8.9 - 13.9	> 250 - 500 > 13.9 - 27.8 hospitalization indicated	> 500 > 27.8
Creatinine increase [1]	> 1 - 1.5 x Baseline > ULN - 1.5 x ULN	> 1.5 - 3.0 x Baseline > 1.5 - 3.0 x ULN	> 3.0 x Baseline > 3.0 - 6.0 x ULN	> 6.0 x ULN
Albumin - Hypoalbuminemia [1] (g/dL) (g/L)	< LLN - 3; < LLN - 30	< 3 - 2; < 30 - 20	< 2 < 20	- -
Alkaline phosphatase increased [1]	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT/AST increase [1]	> ULN - 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Gamma-glutamyl transferase (GGT) increased [1]	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Blood bilirubin increased (total and direct) [1]	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN

Serum Chemistry *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Cholesterol high [1]				
(mg/dL)	> ULN - 300	> 300 - 400	> 400 - 500	> 500
(mmol/L)	> ULN - 7.75	> 7.75 - 10.34	> 10.34 - 12.92	> 12.92
Triglycerides - Hypertriglyceridemia [1]				
(mg/dL)	150 - 300	> 300 - 500	> 500 – 1,000	> 1,000
(mmol/L)	1.71 - 3.42	> 3.42 - 5.70	> 5.70 - 11.40	> 11.4

Abbreviations:

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; GGT = Gamma-glutamyl transferase; LLN = Lower limit of the normal range; ULN = Upper limit of the normal range.

Data source:

1
Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. U.S. Department of Health and Human Services, FDA, National Institutes of Health

National Cancer Institute -. [42]

* The parameters that are not listed and do not have grading categories in the CTCAE will be reviewed by the Principal Investigator or designee and will only be reported as an AE if considered to be clinically relevant.

ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Anemia (Hemoglobin) [1] (g/dL) (mmol) g/L	 < LLN - 10.0 < LLN - 6.2 < 100	 < 10 - 8.0 < 6.2 - 4.9 < 100 - 80	< 8.0 < 4.9 < 80 Transfusion indicated	Life threatening consequences; urgent intervention indicated
Hemoglobin increase (g/dL) [1]	Increase in > 0 - 2 above ULN or above Baseline if Baseline is above ULN	Increase in > 2 - 4 above ULN or above Baseline if Baseline is above ULN	Increase in > 4 above ULN or above Baseline if Baseline is above ULN	-
WBC Decrease (cell/mm^3) [1] 10^{-9}/l	 < LLN – 3,000 < LLN - 3.0	 < 3,000 - 2,000 < 3.0 - 2.0	 < 2,000 - 1,000 < 2.0 - 1.0	 < 1,000 < 1.0
Lymphocytes increase (cell/mm^3) [1]	-	> 4,000 - 20,000	> 20,000	-
Lymphocytes decrease (cell/mm^3) [1] 10^{-9}/l	 < LLN - 800 < LLN - 0.8	 < 800 - 500 < 0.8 - 0.5	 < 500 - 200 < 0.5 - 0.2	 < 200 < 0.2
Neutrophils decrease (cell/mm^3) [1] 10^{-9}/l	 < LLN - 1500 < LLN - 1.5	 < 1500 - 1,000 < 1.5 - 1.0	 < 1000 - 500 < 1.0 – 0.5	 < 500 < 0.5
Platelets decrease - (cell/mm^3) [1] 10^{-9}/l	< LLN – 75,000 < LLN – 75.0	< 75,000 – 50,000 < 75.0 – 50.0	< 50,000 – 25,000 < 50.0 – 25.0	< 25,000 < 25.0

Abbreviations:

LLN = Lower limit of the normal range; ULN = Upper limit of the normal range; WBC = White blood cell.

Data source:

1 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. U.S. Department of Health and Human Services, FDA, National Institutes of Health National Cancer Institute [42]

* The parameters that are not listed and do not have grading categories in the CTCAE will be reviewed by the Principal Investigator or designee and will only be reported as an AE if considered to be clinically relevant.

ABNORMAL LABORATORY VALUES RATING: URINALYSIS PARAMETERS

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Protein [1]	1+ proteinuria; urinary protein < 1.0 g/24 hours	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hours	Urinary protein ≥ 3.5 g/24 hours	-

Abbreviations:

ADL = Activities of daily living; IV = Intravenous.

Data source:

1 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. U.S. Department of Health and Human Services, FDA, National Institutes of Health National Cancer Institute [42]

* The parameters that are not listed and do not have grading categories in the CTCAE will be reviewed by the Principal Investigator or designee and will only be reported as an AE if considered to be clinically relevant.