PHILIP MORRIS PRODUCTS S.A.

Clinical Study Protocol

Study Number:	P1-REXC-10
Study Title:	A randomized, controlled, open-label, 4 parallel arms study to demonstrate reductions in exposure to selected harmful and potentially harmful constituents (HPHC) of cigarette (CIG) smoke in healthy smokers switching to different versions of Tobacco Heating System (THS) compared to continuing CIG smoking, for 5 days in confinement
Short title:	Reduced exposure to HPHC in smokers switching from cigarettes to different versions of THS
Product Name:	THS Blade device THS Induction Mono device THS Induction Mid device
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 3 2000 Neuchâtel, Switzerland
Version:	2.0, Approved
Date:	15 Jul 2022
Authors:	[redacted], PhD, Clinical Scientist [redacted], PhD, Biostatistician [redacted] MD, MSc, Medical Safety Officer

VERSION HISTORY

Version	Date	Protocol Update / Amendment
Original Document 1.0	31 Mar 2022	Not applicable
2.0	15 Jul 2022	Update

Synopsis

Sponsor:

Philip Morris Products S.A.
Quai Jeanrenaud 3
2000 Neuchâtel
Switzerland

Name of Investigational Products:

THS Blade device
THS Induction Mono device
THS Induction Mid device
Subjects' own cigarette brands

Study Title:

A randomized, controlled, open-label, 4 parallel arms study to demonstrate reductions in exposure to selected harmful and potentially harmful constituents (HPHC) of cigarette (CIG) smoke in healthy smokers switching to different versions of Tobacco Heating System (THS) compared to continuing CIG smoking, for 5 days in confinement

Study Number:

P1-REXC-10

Short Title:

Reduced exposure to HPHC in smokers switching from cigarettes to different versions of THS

Primary Objective and Endpoints:

The primary objective is the joint evaluation of the following hypotheses:

1. To demonstrate the reduction of biomarkers of exposure (BoExp) to selected harmful and potentially harmful constituents (HPHC) detailed in Table 1 in smokers switching from CIG to THS Blade device compared to continuing CIG smoking for 5 days.
2. And to demonstrate the reduction of BoExp to selected HPHC detailed in Table 1 in smokers switching from CIG to THS Induction Mono device compared to continuing CIG smoking for 5 days.

3. And to demonstrate the reduction of BoExp to selected HPHC detailed in Table 1 in smokers switching from CIG to THS Induction Mid device compared to continuing CIG smoking for 5 days.

Table 1 List of BoExp Used in the Primary Objective

BoExp	HPHC	Matrix
3-hydroxypropyl mercapturic acid (**3-HPMA**)	Acrolein	Urine[1]
2-cyanoethyl mercapturic acid N-acetyl-S-(2-cyanoethyl)-L-cysteine (**2-CyEMA**)	Acrylonitrile	Urine[1]
Monohydroxybutenyl mercapturic acid (**MHBMA**)	1,3-butadiene	Urine[1]
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (**total NNAL**)	4-(methylnitrosamino)-1-(3-pyridyl)-1-	Urine[1]
Carboxyhemoglobin (**COHb**)	Carbon monoxide (CO)	Blood[2]

[1]BoExp in urine will be expressed as concentration adjusted for creatinine in 24-hour urine;
[2]BoExp in blood expressed as % of saturation of hemoglobin.

Secondary Objectives and Endpoints:

Key secondary objectives

1. To demonstrate the reduction of BoExp to selected HPHC detailed in Table 2 in smokers switching from CIG to THS Blade device compared to continuing CIG smoking for 5 days.
2. To demonstrate the reduction of BoExp to selected HPHC detailed in Table 2 in smokers switching from CIG to THS Induction Mono device compared to continuing CIG smoking for 5 days.
3. To demonstrate the reduction of BoExp to selected HPHC detailed in Table 2 in smokers switching from CIG to Induction Mid device compared to continuing CIG smoking for 5 days.

Table 2 List of BoExp Used in the Key Secondary Objective

BoExp	HPHC	Matrix
S-phenylmercapturic acid (**S-PMA**)	Benzene	Urine[1]
2-hydroxyethylmercapturic acid (**2-HEMA**)	Ethylene oxide	Urine[1]

3-hydroxy-1-methylpropylmercapturic acid (**3-HMPMA**)	Crotonaldehyde	Urine[1]
Total N-nitrosonornicotine (**total NNN**)	N-nitrosonornicotine	Urine[1]
Total 3-hydroxybenzo(a)pyrene (**3-OH-B[a]P**)	Benzo(a)pyrene	Urine[1]
4-aminobiphenyl (**4-ABP**)	4-aminobiphenyl	Urine[1]
2-aminonaphtalene (**2-NA**)	2-aminonaphtalene	Urine[1]

[1]*BoExp in urine expressed as concentration adjusted for creatinine in 24-hour urine*

Other Secondary objective

1. To monitor the safety profile during the study.

   Endpoints
   - Incidents of adverse events (AEs) and serious adverse events (SAEs)
   - Incidence of Device malfunction and product complaints (e.g., events related to charger, holder, or sticks)
   - Vital sign changes from baseline (systolic and diastolic blood pressure, heart rate and respiratory rate)
   - Laboratory safety panel changes from baseline
   - Concomitant medication (ConMed)
   - Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT and QTcF intervals)
   - Spirometry changes from baseline (forced expiratory volume in 1 second [FEV_1], FEV_1 % predicted, forced vital capacity [FVC]), FVC % predicted, FEV_1/FVC)

Exploratory Objectives and Endpoints:

1. To describe the levels of nicotine over the exposure period in smokers switching from CIG to THS Blade device, Induction Mono device, or Induction Mid device, and in smokers continuing to smoke CIG.

   Endpoints (Day -1 to Day 5)

   - Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'hydroxy-cotinine-glucuronide) in 24-hour urine (concentration adjusted for creatinine).

2. To describe daily tobacco product use over the exposure period in smokers switching from CIG to THS Blade device, Induction Mono device, or Induction Mid device, compared to continuing CIG smoking.

Endpoints (Day -1 to Day 5)

- Number of CIG/day
- Number of sticks/day

3. To describe product experience in smokers switching from CIG to THS Blade device, Induction Mono device, or Induction Mid device compared to smokers continuing CIG smoking.

   Endpoints (Day -1 to Day 5)

   - Subscale scores of Product Experience (ABOUT–Product Experience) questionnaire

The estimands requested as per ICH guidelines [1] for all objectives will be described in the corresponding statistical protocol sections.

Study Hypothesis:

The primary hypothesis tested in this study is that BoExp considered for the primary objective will be significantly reduced for each THS variant (Blade device, or Induction Mono device, or Induction Mid device, respectively) in subjects who adhere to switching for 5 days to using THS, compared to subjects continuing CIG smoking.

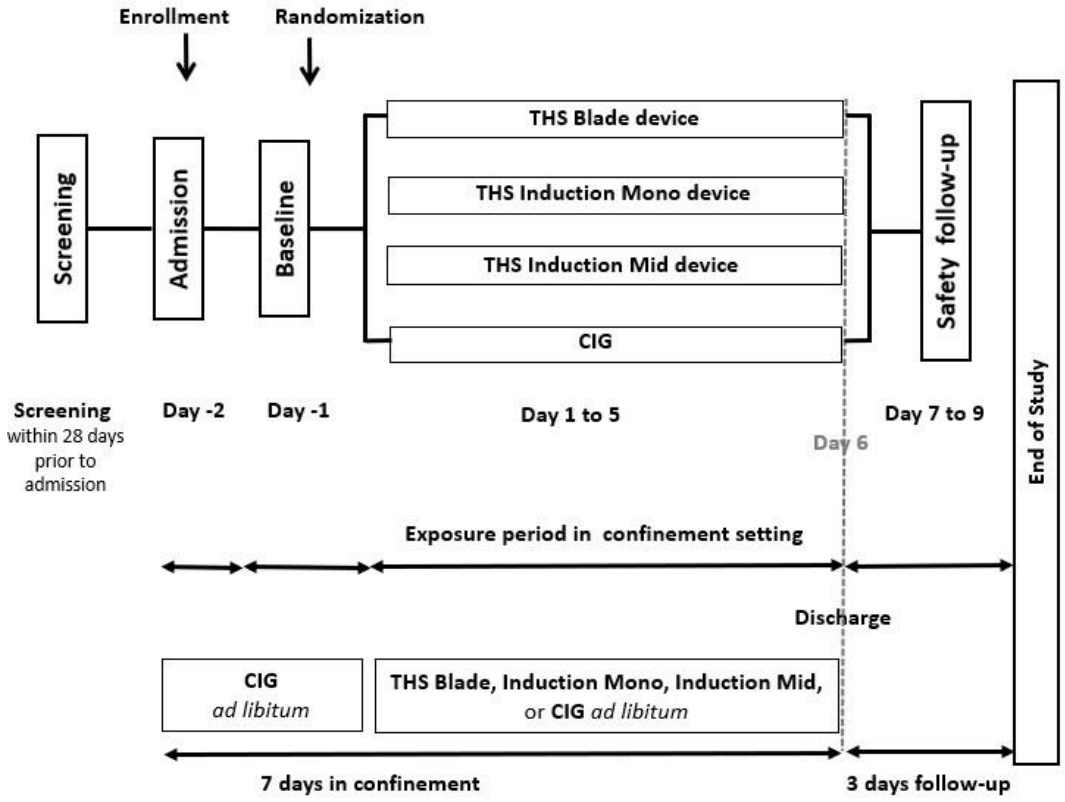
A set of key secondary hypothesis based on a set of BoExp considered for secondary objectives will be tested using a hierarchical approach to show significant reduction in subjects who adhere switching for 5 days to one of the THS variants (Blade device, Induction Mono device, or Induction Mid device) compared to subjects continuing CIG.

Study Design:

This is a randomized, controlled, open-label, 4 parallel arms study with a stratified randomization by sex (a quota for each sex (females and males) of at least 40% overall).

This is an *ad libitum* use/smoking study. During confinement, in general, THS use and CIG consumption (according to randomization) will be allowed between 06:30 AM and 11:00 PM.

During the confinement period, adherence to product arm allocation (exclusive use of THS Blade device, or Induction Mono device, or Induction Mid device, or CIG) will be ensured by strict distribution of the devices, and of each stick/CIG upon demand of the subject to the site staff.



Abbreviations:
CIGs = Cigarettes; THS = Tobacco Heating System

Figure 1 Study Design

Screening period (from Day -30 to Day -3, prior to admission):

The screening period covers up to four weeks prior to admission. A demonstration of the THS Blade device, Induction Mono device, and Induction Mid device will be done by the site staff during the Screening visit. Screening procedures do not necessarily have to be conducted on the same day. All subjects will receive information on the risks of smoking, smoking cessation advice, and briefing on THS. Eligible subjects will return to the investigational site for verification of eligibility at Admission.

Admission (admission on Day -2 until 06:29 AM of Day -1):

Subjects will be in a confinement setting for 7 days from Day -2 onwards.

Subjects will be enrolled if all eligibility criteria are met. Only adult subjects willing and able to use the products will be enrolled in the study.

CIG smoking will be allowed *ad libitum* from the time of admission of the subject until approximately 11:00 PM of Day -2, except before/during assessments requiring smoking breaks. Use of any tobacco and/or nicotine containing product (TNP) other than CIG (and THS Blade device and Induction Mono device for the product test) will not be allowed on Day -2 after admission.

On Admission Day -2, as the last procedure of the eligibility assessments, subjects will have a product test of the THS Blade device and Induction Mono device (use of up to three sticks per device), prior to enrolment. In female subjects, the THS product tests will only be performed once pregnancy is excluded by a negative pregnancy test. After the product test, subjects not willing to use THS during the study will be discontinued and will be replaced. Subjects willing to continue participation will start their confinement period.

Baseline (Day -1, 06:30 AM until Day 1, 06:29 AM):

Subjects may continue smoking their CIG *ad libitum,* except before/during assessments requiring smoking breaks. The 24-hour urine collection for Day -1 will start in the morning of Day -1 (details provided in Appendix A). Baseline assessments will be performed as indicated in Appendix A.

Eighty subjects will be randomized to one of the 4 study arms in a 1:1:1:1 ratio using a stratified randomization by sex with a minimum of 40% of each sex (male and female) overall:

- THS Blade device: *ad libitum* use of Blade Regular sticks.
- THS Induction Mono device: *ad libitum* use of the Induction Regular sticks.
- THS Induction Mid device: *ad libitum* use of the Induction Regular sticks.
- CIG: *ad libitum* use of their preferred regular CIG brand.

Subjects will be informed of their randomized study arm by the study site staff on Day 1 prior to 06:30 AM.

Exposure in confinement (Day 1, 06:30 AM until Day 5, 11:00 PM):

The Exposure period will consist of 5 days of *ad libitum* use of the assigned investigational products (one out of the 3 versions of THS or CIG) between 06:30 AM and 11:00 PM. Use of any TNP other than the assigned investigational product will not be allowed and may, at the discretion of the Investigator(s), result in discontinuation of the subject from the study.

Daily 24-hour urine will be collected from Day -1 to Day 5. On Day 1, product use must not start before the end of 24-hour urine collection of Day -1. The 24-hour urine collection period for Day 5 will end in the morning of Day 6 prior to discharge.

During the confinement period, site staff will distribute assigned investigational products to the subjects and record all products distributed in the source documentation.

Discharge period (Day 5, 11:01 PM until Day 6, time of Discharge):

Discharge procedures according to the schedule given in Appendix A will be conducted to complete the Discharge of the subject from the clinic after 7 days in a confined setting. Use of CIG will be allowed on Day 6 once all study procedures are completed.

Safety follow-up (Day 6, time of Discharge, to Day 9):

After Discharge on Day 6, subjects will enter a 3-day Safety follow-up period during which AEs/SAEs will be collected and follow-up of any ongoing AEs/SAEs will be conducted by the investigational site. The End of the study (EOS) is defined as the completion of the 3-day Safety follow-up period either after the Discharge on Day 6, or after Early termination.

During the study, subjects in the CIG arm and the THS arms who want to quit smoking will receive appropriate medical advice and will be referred to a smoking cessation counsellor. This will not affect subject's financial compensation, and the subject will remain in the study.

Biobanking:

If the subject consents, additional samples will be taken from the 24-hour urine collection for long-term biobanking (two years at most) in view of further measurements of BoExp and stored at the bioanalytical laboratory(Appendix B).

Study Population and Main Criteria for Inclusion/Exclusion:

A sufficient number of healthy adult female and male smokers who meet all the following inclusion and exclusion criteria will be enrolled into the study to ensure that 80 subjects will be randomized:

Inclusion Criteria	Screening	Day -2
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	X	
2. Subject is male or female and between 21 and 65 years old (inclusive).	X	
3. Subject has been a smoker for ≥3 years prior to the screening visit (smoking cessation attempts during this period, if any, did not last > 6 months in total).	X	X
4. Subject has continuously smoked on average ≥10 commercially available regular CIGs/day over the last 4 weeks[a]. Smoking status will be verified based on a urinary cotinine test (cotinine ≥200 ng/mL).	X	X
5. Subject is healthy as judged by the Investigator based on available assessments from the screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, and medical history).	X	
6. Subject does not plan to quit smoking within the next three months.	X	X

a. Users of other TNP in addition to CIG smoking may be enrolled into the study if they agree to limit themselves to stick use/CIG smoking (according to their randomization) during the Exposure period

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

Exclusion Criteria	Screening	Day -2
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).	X	
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., in emergency situations, under guardianship, prisoners).	X	

3. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or any other medical condition (including safety laboratory), which as per the judgment of the Investigator would jeopardize the safety of the subject.	X	
4. Subject experienced within 30 days prior to screening/admission a body temperature >37.5°C or an acute illness (e.g., upper respiratory-tract infection, viral infection, etc.) or the subject has a confirmed or suspected active COVID-19 infection (based on the signs and symptoms observed at the time of assessment).	X	X
5. As per the Investigator's judgment, the subject has medical conditions which do or will require a medical intervention (e.g., start of treatment, surgery, hospitalization) during the study participation, which may interfere with the study participation and/or study results.	X	
6. Subject has relevant history of, or current asthma condition or COPD condition, and/or clinically significant findings.	X	
7. Subject has donated blood or received whole blood or blood products within 3 months.	X	
8. BMI < 18.5 kg/m^2 or ≥ 32.0 kg/m^2.	X	
9. Positive serology test for HIV 1/2, HBV, or HCV[a].	X	
10. Subject has a positive alcohol breath test and/or has a history of alcohol disorder that could interfere with their participation in the study.	X	
11. The subject has a positive urine drug test.	X	
12. Subject or one of their family members[b] is a current or former employee of the tobacco or e-cigarette industry.	X	
13. Subject or one of their family members[b] is an employee of the investigational site or of any other parties involved in the study.	X	

14. Subject has participated in another clinical study within 3 months.	X	
15. Subject has been previously screened or enrolled in this study.	X	
16. Subject is pregnant (does not have negative pregnancy tests at screening and at admission) or is breastfeeding.	X	X
17. For women of childbearing potential only[c]: subject does not agree to use an acceptable method of effective contraception[d].	X	

a. Human immunodeficiency virus, hepatitis B virus, hepatitis C virus

b. As defined by FDA guidance on Human Subject Protection (21 CFR 50.3(l), (m), 50.24(a)(6), (a)(7)(v), b)): "Family member" means among other things "parent", "spouse", "brothers, sisters, and spouses of brothers and sisters" and "any individual related by affinity…whose close association with the subject is equivalent of a family relationship"

c. Women who are not of childbearing potential meet at least one of the following criteria:
   - Have undergone hysterectomy or bilateral tubal ligation,
   - Have medically confirmed ovarian failure, or
   - Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

d. Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety follow-up period.

Sample Size and Evaluation:

In this study, 80 healthy adult smokers will be randomized in a 1:1:1:1 randomization ratio to:

- THS Blade device arm
- THS Induction Mono device arm
- THS Induction Mid device arm
- CIG arm

This setting will provide more than 90% power to the trial to demonstrate a reduction for all BoExp tested in the primary objective for all THS study arms compared to the CIG arm, using a one-sided two-sample t-test with 2.5% type I error probability. This will also account for 15% data point loss due to missing, non-analyzable sample or major protocol deviation impacting evaluability of the primary objectives. This assumes, based on a similar study conducted by PMP S.A. (see ClinicalTrials.gov Identifier: NCT01959932), that the geometric mean ratio (GM) and the related geometric coefficient of variation (GCV) of the ratio between all the THS study arms and the CIG arm are the following:

- GMR = 23.45% and GCV = 16.84% for COHb at Day 5,
- GMR = 41.63% and GCV = 26.10% for 3-HPMA at Day 5,
- GMR = 13.16% and GCV = 34.41% for 2-CyEMA at Day 5,
- GMR = 43.54% and GCV = 27.13% for total NNAL at Day 5,
- GMR = 12.58% and GCV = 76.92% for MHBMA at Day 5.

Investigational Products; Dose; and Mode of Administration:

Investigational Products:

Tobacco Heating System (THS) devices, together with corresponding sticks, will be provided by the sponsor, whereas for the CIG arm, subjects will provide their own supply of commercially available preferred single brand regular (non-mentholated) CIG, for the study duration:

Investigational product	Stick
THS Blade device	Blade Regular sticks
THS Induction Mono device	Induction Regular sticks
THS Induction Mid device	Induction Regular sticks
CIG (Cigarette, non-mentholated)	Not applicable

During product testing on Day -2, subjects will be able to familiarize themselves with THS Blade device and THS Induction Mono device (considering that product experience with THS Induction Mono device will be very comparable to THS Induction Mid device). Only one variant of sticks will be tested (Regular).

Duration of Study:

The entire study duration per subject will be 12 to 39 days. This will include a Screening period of up to 28 days prior to Admission (Day -30 to Day -3), followed by a 7-day confinement period (Admission Day -2, Baseline Day -1, Exposure Day 1 to Day 5), followed by Discharge on Day 6, and a 3-day Safety follow-up period until and including Day 9.

The End of the study (EOS) for a subject is defined as the completion of the 3-day Safety follow-up period either after the Discharge at Day 6, or after the Early termination of the subject. The end of the whole study corresponds to the EOS of the last subject.

Statistical Methods:

Analysis Sets:

The Full Analysis Set (FAS) will consist of all randomized subjects who have at least one post-randomization product use experience (if randomized to CIG or one of the THS arms) and who have at least one valid non-safety assessment. The FAS will be analyzed by randomized study arm.

The Per Protocol Set (PP) will be a subset of FAS and will include all randomized subjects who fulfil key compliance criteria of the protocol and have no major protocol deviation impacting the evaluability of the primary objective. The PP will be analyzed by randomized study arm.

The safety population (SAF) will consist of all the subjects enrolled in the study with at least one exposure to investigational product (product test at Admission Day -2), and who have at least 1 valid value for a safety assessment. The SAF will be analyzed according to actual exposure arm.

Additional analysis sets may be defined in the SAP.

Statistical Analysis:

The BoExp tested in the primary objective (Table 1) will be analyzed using a linear mixed model for repeated measurements separately on the log scale for each THS study arm. A 1-sided pairwise test will compare in the PP set for each THS version the reduction in BoExp in subjects switching from CIG to THS, compared to continuing CIG smoking.

Descriptive statistics will be presented at each timepoint, where applicable. Descriptive statistics will be presented for each arm separately.

The other BoExp, including the ones related to key secondary objectives, will be analyzed using a similar model to the primary analysis. Product use and questionnaires will be summarized using descriptive statistics.

Safety endpoints will be reported by list and descriptive statistics will be produced. AE data will serve for the assessment of the safety.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

List of In-Text Figures

List of Appendices

Abbreviations and Definitions of Terms

Abbreviations

2-CyEMA	2-Cyanoethyl mercapturic acid *N*-Acetyl-*S*-(2-cyanoethyl)-L-cysteine
2-HEMA	2-hydroxyethylmercapturic acid
2-NA	2-aminonaphtalene
3-HMPA	3-hydroxypropylmercapturic acid
3-HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-OH-B[a]P	Total 3-hydroxybenzo(a)pyrene
4-ABP	4-aminobiphenyl
ABOUT	Assessment of behavioral outcomes related to tobacco and nicotine products
AE	Adverse event
ATS	American thoracic society
BMI	Body mass index
BoExp	Biomarker of exposure
BP	Blood pressure
CAF	Caffeine
CDISC	Clinical data interchange standards consortium
CFR	Code of federal regulations
CI	Confidence interval
CIG	Conventional cigarette(s)
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTMS	Clinical trial management system
CV (statistics)	Coefficient of variation
DM-CRO	CRO responsible for data management activities
DMP	Data management plan
DVP	Data validation plan
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ERS	European respiratory society
FAS	Full analysis set
FDA	Food and Drug Administration

FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCV (statistics)	Geometric coefficient of variation
GMR (statistics)	Geometric mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPHC	Harmful and potentially harmful constituents
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational product
ITT	Intention to treat
IxRS	Interactive web/voice response system
LLOQ	Lower limit of quantification
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MHBMA	Monohydroxybutenyl mercapturic acid
NCT	ClinicalTrials.gov identifier
NEQ	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
PMP	Philip Morris Products S.A.
PP	Per protocol set
PX	Paraxanthine
QC	Quality control
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical analysis system
SDTM	Study data tabulation model
SFTP	Secure file transfer protocol
SHM	Sample handling manual
SOC	System organ class
SOP	Standard operating procedure
S-PMA	*S*-phenylmercapturic acid

THS	Tobacco Heating System
TNP	Tobacco and/or nicotine containing product
ULOQ	Upper limit of quantification
USA	United states of America
WBC	White blood cell (count)
WHO	World Health Organization
WOCBP	Women of child-bearing potential

Explanation of Terms

The following special terms are used in this protocol:

Alternate subjects	Subjects who have signed the ICF, have met the inclusion and exclusion criteria, and have been enrolled (completing Screening visit and Admission Day -2), but did not proceed to Baseline Day -1 and have not been randomized due to a sufficient number of subjects available for randomization at that time. An alternate subject may join the following group if her/his 28-day Screening period has not exceeded. The alternate subject will have to repeat the Admission Day -2 visit to re-confirm eligibility.
Blade device	Tobacco Heating System (THS) device with Blade technology for Blade stick use
Blade stick	Tobacco stick designed specifically to be used with the Blade device.
Cigarette(s) (CIG)	The term 'CIG' refers to commercially available regular cigarettes (manufactured) and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Early termination	Premature termination of exposure to the Investigational Product after the start of the Exposure period in the confinement setting.
End of study (EOS)	The EOS for an exposed subject is defined as the completion of the 3-day Safety follow-up period either after Discharge on Day 6, or after the date of an Early termination, or after discontinuation of the exposed subject. The EOS of the entire study is the end of the Safety Follow-up Period for the last subject.
Induction Mono device	Tobacco Heating System (THS) device with Induction technology (combined Charger-Holder device for Induction stick use).
Induction Mid device	Tobacco Heating System (THS) device with Induction technology (device with Induction stick Holder for Induction stick use and separate Charger).
Induction stick	Tobacco stick designed specifically to be used with the Induction Mono device or Induction Mid device.

Randomization	Allocation of the respective product at any time on Day -1 utilizing an interactive web and voice response system (IxRS). On Day 1, the subjects will be individually informed about the product they are randomized to prior to the first product use.
Screening failure	All subjects that are not enrolled are considered as screen failures. Re-screening of subjects who did not meet any entry criteria will not be permitted.
Stick	Refers to either Induction or Blade stick if not specified.
THS	In this protocol, the term THS generally includes use of any of the devices to be tested (i.e., Induction Mid device or Induction Mono devices or Blade device) with their respective tobacco sticks.

1. Ethics and Regulations

1.1 Independent Ethics Committee (IEC) 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 Investigator(s)) and/or other evidence of qualifications and any other documents requested by an Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC. The IEC shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Good Clinical Practice (GCP) [2] and local requirements, as applicable.

In accordance with GCP, a written confirmation of the IEC approval should be provided to the Sponsor. This should identify the study (name of the Investigator(s), study number, and title) and the documents that have been approved by the IEC, with dates and version numbers, as well as the date of approval. The composition of the IEC, 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 IEC will be filed in the Investigator site 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 IEC.

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 IEC, and substantial amendments will only be implemented after approval by the IEC.

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

Relevant safety information will be submitted to the IEC during the study 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 Investigator(s) agree(s) to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IEC. The Investigator(s) and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki will be filed in the Investigator site file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before or at Screening visit, the Investigator(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 study, and the Investigator(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 his/her participation 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 informed consent discussion during Screening visit will both sign, date and time the ICF. The ICF includes both the subject information sheet and the informed consent. No study-specific procedures will be performed before the ICF has been signed (including date and time).

In addition to consenting to study participation, the subjects will be asked for their consent to the storage of urine samples for long-term biobanking (two years at most), i.e., the storage of samples from the 24-hour urine collection at the bioanalytical laboratory (Appendix B), in view of further measurements of BoExp. These analyses are not described in the protocol or statistical analysis plan (SAP) and will not be included in the clinical study report (CSR), but in a separate report.

The subject's consent to urine sample biobanking is not a requirement for the study participation and the subject's participation in the study does not depend on their consenting to biobanking.

The original, dated and signed ICF(s) must be kept by the Investigator(s) and filed in the Investigator site file 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 in writing.

Subjects 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 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 Investigator(s) will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by the relevant IEC 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 participation or are discontinued from the study will be informed by letter, email, or phone call.

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, and Investigator(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 with products such as THS devices. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [3].

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette (CIG) smoking causes pulmonary, cardiovascular and other serious diseases in smokers [4]. There is no safe CIG, and the best option for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks that are attributable to smoking, some smokers decide to continue smoking. The development of novel tobacco and/or nicotine containing products (TNPs) with the potential to be less harmful as potential alternatives to CIG smoking represents an approach to reduce cigarette-related deaths and diseases among smokers [5].

Philip Morris Products S.A. (PMP) is developing such alternative products that have the potential to reduce individual risk and population harm in comparison to smoking CIG. These products aim to substantially reduce or eliminate the exposure to HPHC generated from CIG smoke (except nicotine), while providing an acceptable substitute for CIG smoking and lowering the health risk. When developing new products such as Tobacco Heating Systems (THS), appropriate assessment including comprehensive understanding of product characterization, its safety, and related impact of product use in humans is critical.

2.1.2 Description of the Product and Scientific Findings

Several versions of the THS devices and of sticks specifically designed for these products are now available on the market. They all consist of at least a charging unit(s) (either one single integrated charger-holder system, or a separate charger and a separate stick holder) used to heat a stick. Some charging units are required to be charged between every use, and some have a larger battery, allowing several consecutive uses. Further details are provided in the Investigator's Brochure [6].

PMP has developed THS products either with Blade heating technology or Induction heating technology (marketed under the name of IQOS™ or ILUMA™, respectively). The Blade device is heating Blade sticks with a heating blade technology, while the Induction Mono device and the Induction Mid device do heat Induction sticks by using the heat induction technology. Independently of the technology, the temperature of the stick heating is controlled during the use to avoid burning of the tobacco.

Specific sticks have been developed for THS Blade devices and Induction devices, called Blade sticks and Induction sticks, respectively. The sticks to be used with the Blade

technology are not compatible with the Induction technology, and vice versa. Only one flavor variant of the sticks (Regular, i.e., tobacco flavor) will be tested in this study.

PMP has conducted an exhaustive pre-clinical and clinical assessment of the THS Blade device. In 2020, the FDA authorized the Blade device (IQOS™) to be marketed as a Modified Risk Tobacco Product with exposure modification orders [7]. PMP is now planning to demonstrate that using the new versions of THS, including the Induction Mono devices and Induction Mid device, will lead to comparable levels of reduction of exposure to selected HPHC in smokers switching exclusively to either one of these products.

2.2 Anticipated Benefits and Risks

2.2.1 Anticipated Benefits

Information on health risks associated with smoking, and smoking cessation advice, will be provided at the Screening visit, the Admission visit on Day -2, and at Discharge on Day 6, respectively. The advice will follow the recommendations of the World Health Organization (WHO) "Evidence based Recommendations on the Treatment of Tobacco Dependence" [8]. Subjects who are motivated to quit smoking during the study will be encouraged to do so and will be referred to appropriate medical services for necessary support and counselling. Subjects who participate in this study will also benefit from repeated and detailed health check-ups.

2.2.2 Anticipated Foreseeable Risks due to Study Procedures

The potential risk of scheduled procedures in the present study (e.g., blood samples) are deemed to be on par with procedures routinely performed during normal or extended health examinations by the subject's healthcare professional. The total volume of blood to be drawn is approximately 95 mL and does not exceed the levels for a standard blood donation. The risks related to blood sampling include for example: excessive bleeding, fainting, hematoma, paresthesia, or infection, and those related to the total amount of blood taken over a time span such as weakness, dizziness, or anemia.

2.2.3 Anticipated Foreseeable Risks due to Investigational Products

An adult smoker using a THS device or CIG may experience:

- Transient nicotine withdrawal symptoms (e.g., urge to smoke, irritability, anxiety feelings, restlessness, and difficulty to concentrate) as similar to cravings observed during smoking cessation
- Transient symptoms suggesting mild nicotine overdose such as stimulatory effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, and decreased ability to concentrate), gastric acid secretion, and vomiting. Individuals who experience adverse events (AEs) (suggesting

excessive stimulant effects) should be instructed to reduce their intensity of product use by decreasing the number of puffs and/or the intensity of puffing

- Change in smoking habits due to study requirements and related concomitant symptoms, e.g., craving.

Medical supervision of all study subjects with follow-up of those who have experienced adverse events/serious adverse events (AEs/SAEs).

2.2.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detail to study participants. Unexpected malfunction of any of the THS devices may lead to unforeseeable risk. Risk mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 Study Objectives

The estimands requested as per ICH guidelines [1] for all objectives are listed in section 12.5.1 for the primary objective, and section 12.5.2 for secondary objectives.

3.1 Primary Objective

The primary objective of this study is the joint evaluation of the following hypotheses:

1. To demonstrate the reduction of biomarkers of exposure (BoExp) to selected harmful and potentially harmful constituents (HPHC) detailed in Table 3 in smokers switching from CIG to THS Blade device compared to continuing CIG smoking for 5 days.
2. And to demonstrate the reduction of BoExp o selected HPHC detailed in Table 3 in smokers switching from CIG to THS Induction Mono device compared to continuing CIG smoking for 5 days.
3. And to demonstrate the reduction of BoExp to selected HPHC detailed in Table 3 in smokers switching from CIG to THS Induction Mid device compared to continuing CIG smoking for 5 days.

Table 3 List of BoExp Used in the Primary Objective

BoExp	HPHC	Matrix
3-hydroxypropyl mercapturic acid (**3-HPMA**)	Acrolein	Urine[1]
2-cyanoethyl mercapturic acid N-acetyl-S-(2-cyanoethyl)-L-cysteine (**2-CyEMA**)	Acrylonitrile	Urine[1]
Monohydroxybutenyl mercapturic acid (**MHBMA**)	1,3-butadiene	Urine[1]
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (**total NNAL**)	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	Urine[1]
Carboxyhemoglobin (**COHb**)	Carbon monoxide (CO)	Blood[2]

[1]BoExp in urine will be expressed as concentration adjusted for creatinine in 24-hour urine;
[2]BoExp in blood expressed as % of saturation of hemoglobin.

3.2 Key Secondary Objectives

1. To demonstrate the reduction of BoExp to selected HPHC detailed in Table 4 in smokers switching from CIG to THS Blade device compared to continuing CIG smoking for 5 days.

2. To demonstrate the reduction of BoExp to selected HPHC detailed in Table 4 in smokers switching from CIG to THS Induction Mono device compared to continuing CIG smoking for 5 days.
3. To demonstrate the reduction of BoExp to selected HPHC detailed in Table 4 in smokers switching from CIG to THS Induction Mid device compared to continuing CIG smoking for 5 days.

Table 4 List of BoExp Used in the Key Secondary Objective

BoExp	HPHC	Matrix
S-phenylmercapturic acid (**S-PMA**)	Benzene	Urine[1]
2-hydroxyethylmercapturic acid (**2-HEMA**)	Ethylene oxide	Urine[1]
3-hydroxy-1-methylpropylmercapturic acid (**3-HMPMA**)	Crotonaldehyde	Urine[1]
Total N-nitrosonornicotine (**total NNN**)	N-nitrosonornicotine	Urine[1]
Total 3-hydroxybenzo(a)pyrene (**3-OH-B[a]P**)	Benzo(a)pyrene	Urine[1]
4-aminobiphenyl (**4-ABP**)	4-aminobiphenyl	Urine[1]
2-aminonaphtalene (**2-NA**)	2-aminonaphtalene	Urine[1]

[1]*BoExp in urine expressed as concentration adjusted for creatinine in 24-hour urine*

3.3 Other Secondary Objective

1. To monitor the safety profile during the study.

   Endpoints
   - Incidents of adverse events (AEs) and serious adverse events (SAEs)
   - Incidence of device malfunction and product complaints (e.g., events related to device or sticks)
   - Vital sign changes from baseline (systolic and diastolic blood pressure, heart rate and respiratory rate)
   - Laboratory safety panel changes from baseline
   - Concomitant medication (ConMed) changes from baseline
   - Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, and QTcF intervals)
   - Spirometry changes from baseline (forced expiratory volume in 1 second [FEV_1], FEV_1 % predicted, forced vital capacity [FVC], FVC % predicted, FEV_1/FVC)

3.4 Exploratory Objectives

1. To describe the levels of nicotine over the exposure period in smokers switching from CIG to THS Blade device, Induction Mono device, or Induction Mid device, and in smokers continuing to smoke CIG.

   Endpoints (Day -1 to Day 5)

   - Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'hydroxy-cotinine-glucuronide) in 24-hour urine (concentration adjusted for creatinine).

2. To describe daily tobacco product use over the exposure period in smokers switching from CIG to THS Blade device, Induction Mono device, or Induction Mid device, compared to continuing CIG smoking.

   Endpoints (Day -1 to Day 5)

   - Number of CIG/day
   - Number of sticks/day

3. To describe product experience in smokers switching from CIG to THS Blade device, Induction Mono device, or Induction Mid device compared to smokers continuing CIG smoking.

   Endpoints (Day -1 to Day 5)

   - Subscale scores of Product Experience (ABOUT–Product Experience) questionnaire.

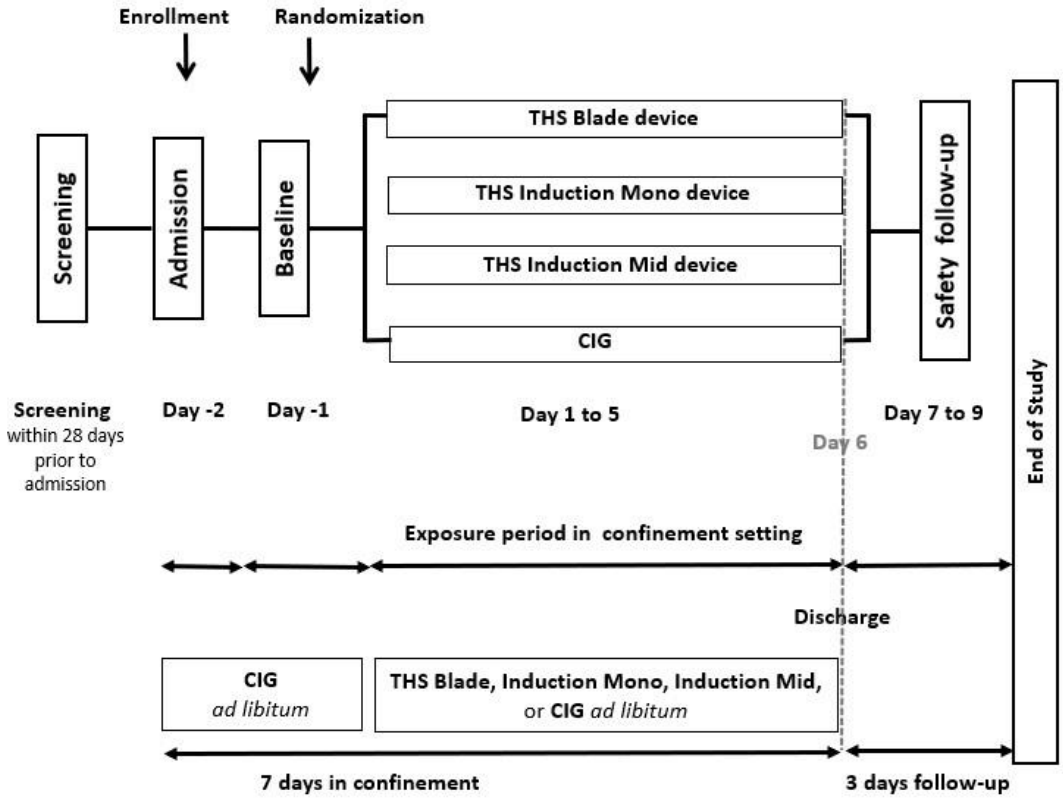
4 Investigational Plan

4.1 Overall Study Design and Plan

This is a randomized, controlled, open-label, 4 parallel arms study with a stratified randomization by sex (a quota for each sex (females and males) of at least 40% overall).

This is an *ad libitum* use/smoking study. During confinement, in general, THS use and CIG consumption (according to randomization) will be allowed between 06:30 AM and 11:00 PM.

During the confinement period, adherence to investigational product arm allocation (exclusive use of THS devices with designated sticks, or CIG smoking, respectively) will be ensured by strict distribution of the devices, and of each stick/CIG upon demand of the subject to the site staff.



Abbreviations:
CIGs = Cigarettes; THS = Tobacco Heating System

Figure 2 Study Design

Screening period (from Day -30 to Day -3, prior to admission):

The screening period covers up to four weeks prior to admission. A demonstration of the THS investigational products will be done by the site staff during the Screening visit. Screening procedures do not necessarily have to be conducted on the same day. All subjects will receive information on the risks of smoking and smoking cessation advice and briefing on THS. Eligible subjects will return to the investigational site for verification of eligibility at Admission.

Admission (admission on Day -2 until 06:29 AM of Day -1):

Subjects will be in a confinement setting for 7 days from Day -2 onwards.

Subjects will be enrolled if all eligibility criteria are met. Only subjects willing and able to use the products will be enrolled in the study.

CIG smoking will be allowed *ad libitum* from the time of admission of the subject until approximately 11:00 PM of Day -2, except before/during assessments requiring smoking breaks. Use of any tobacco and/or nicotine containing product (TNP) other than CIG (and THS during the product test) will not be allowed on Day -2 after admission.

On Admission Day -2, as the last procedure of the eligibility assessments, subjects will have a product test of the THS Blade device and Induction Mono device (use of up to three sticks per device), prior to enrolment. In female subjects, the THS product tests will only be performed once pregnancy is excluded by a negative pregnancy test. After the product test, subjects not willing to use THS during the study will be discontinued and will be replaced. Subjects willing to continue participation will start their confinement period.

Provided that the 28-day Screening period is not exceeded, alternate subjects (that have not performed Baseline Day -1 nor have been randomized formerly) have to repeat the Admission visit of the following group to re-confirm their eligibility for randomization.

Baseline (Day -1, 06:30 AM until Day 1, 06:29 AM):

Subjects may continue smoking their CIG *ad libitum,* except before/during assessments requiring smoking breaks. The 24-hour urine collection for Day -1 will start in the morning of Day -1 (details provided in Appendix A). Baseline assessments will be performed as indicated in Appendix A.

Subjects will be randomized to one of the 4 study arms (THS Blade device, THS Induction Mono device, THS Induction Mid device, or CIG) in a 1:1:1:1 ratio using a stratified randomization.

Subjects will be informed of their randomized study arm by the study site staff on Day 1 prior to 06:30 AM.

Exposure in confinement (Day 1, 06:30 AM until Day 5, 11:00 PM):

The exposure period will consist of 5 days of *ad libitum* use of the assigned investigational product between 06:30 AM and 11:00 PM in the THS and CIG arms. Use of any TNP other than the assigned investigational product (or CIG smoking in the CIG arm) will not be allowed and may, at the discretion of the Investigator, result in discontinuation of the subject from the study.

Daily 24-hour urine will be collected from Day 1 to Day 5. On Day 1, product use must not start before the end of 24-hour urine collection of Day -1. The 24-hour urine collection period for Day 5 will end in the morning of Day 6 prior to discharge.

During the confinement period, site staff will distribute assigned products to the subjects and record all products distributed in the source documentation.

Discharge period (Day 5, 11:01 PM until Day 6, time of Discharge):

Discharge procedures, including laboratory parameters, will be conducted to discharge the subject from the clinic after 7 days in a confined setting. Use of CIG will be allowed on Day 6 once all study procedures are completed.

Safety follow-up (Day 6, time of Discharge, to Day 9):

After Discharge on Day 6, or after Early termination, subjects will enter a 3-day Safety follow-up period during which AEs/SAEs will be collected and follow-up of any ongoing AEs/SAEs will be conducted by investigational site. The end of the study is defined as the completion of the 3-day Safety follow-up period either after the Discharge on Day 6, or after Early termination.

During the study, subjects in the CIG arm and the THS arms who want to quit smoking will receive appropriate medical advice. This will not affect subject's financial compensation, and the subject will remain in the study.

4.2 Rationale for Study Design

This clinical study aims to demonstrate the reduction of BoExp to selected HPHC in smokers switching from CIG to each of the THS variants with different heating technology (Blade device, or Induction Mono device, or Induction Mid device, respectively), compared smokers who continue to smoke CIG. A reduction of exposure to HPHC derived from CIG smoke is expected to reduce the health risk of CIG consumption if switching completely to THS.

The exposure period in confinement will provide information on exposure reductions achievable in a well-controlled environment with full control on daily THS stick consumption and compared to CIG smoking.

HPHC of cigarette smoke considered to be of health concern have been reported by different regulatory bodies and health organizations [9, 10]. Lists of HPHC to be reported in cigarette smoke have consequently been developed, as described, for example in the FDA draft guidance on "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke" [11].

It is not possible to measure each of those potentially toxic constituents in humans, due to constraints in availability of validated, reliable methods, or simply the absence of suitable BoExp. A selection of HPHC to be evaluated in this study was thus performed based on the following criteria:

1. The HPHC selected are representative of a variety of chemical classes and organ toxicity classes as defined by the FDA (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, and addiction potential) [10]
2. The HPHC selected reflect on a specific toxic exposure or are a reliable surrogate of exposure to HPHC
3. The HPHC assessed cover a broad range of formation temperatures
4. The HPHC are specific to smoking with other sources being minor or non-existent
5. The BoExp to a HPHC is reliably detectable using validated, reproducible, precise analytical methods
6. The BoExp to a HPHC has a half-life that is suitable with the schedule of assessments.

Other parameters such as product evaluation, and subjective effects related to smoking including smoking urges will be evaluated.

Twenty-four hours urine collection conducted in this study is the standard method to measure the levels of excretion of BoExp.

All subjects in the CIG arm will be asked to buy their own CIG according to their anticipated needs for the study to minimize any changes in their smoking behavior.

4.3 Appropriateness of Measurements

All laboratory measures utilized for this study are validated and are appropriate for the study assessments.

The ABOUT-Product Experience, the self-report measure to be used in this study, has been developed following the best practices (including the FDA's Guidance for Industry Patient-Reported Outcome (PRO) Measures [12]), which provide the scientific basis for the development, modification, and validation of PRO measures in support of clinical and regulatory research. The FTND [13, 14] and the ABOUT-Product Experience questionnaires [15, 16] to be used in this study are validated and previously published or adapted versions of validated questionnaires.

4.4 Study Duration

The entire study duration per subject will be at least 12 and at most 39 days. This will include a screening period of up to 28 days prior to admission (Day -30 to Day -3), followed by a 7-day confinement period (Day -2 to Day 5), Discharge on Day 6, and a 3-day Safety follow-up period until and including Day 9.

The EOS for an exposed subject is defined as the completion of the 3-day Safety follow-up period following either after Discharge on Day 6, or after the date of Early termination of the subject, or after the discontinuation of the exposed subject. The EOS of the entire study is the end of the Safety follow-up period for the last subject.

5 Study Population

Eighty smoking healthy female or male adult subjects who have smoked on average at least 10 regular CIGs per day for the last 4 weeks prior to Admission will be randomized (stratified by sex) using a 1:1:1:1 ratio into this study. Quotas will be applied to ensure that the randomized population contains at least 40% of both sexes (males and females) overall.

The maximum number of CIG smoked daily is not limited. Subjects must have been smoking for at least 3 years prior to the Screening visit. There will be no brand restrictions of CIG (non-mentholated only). Smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/mL).

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria can be enrolled into the study:

Inclusion Criteria	Screening	Day -2
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	X	
2. Subject is male or female and between 21 and 65 years old (inclusive).	X	
3. Subject has been a smoker for ≥3 years prior to the screening visit (smoking cessation attempts during this period, if any, did not last > 6 months in total).	X	X
4. Subject has continuously smoked on average ≥10 commercially available regular CIGs/day over the last 4 weeks[a]. Smoking status will be verified based on a urinary cotinine test (cotinine ≥200 ng/mL).	X	X
5. Subject is healthy as judged by the Investigator based on available assessments from the screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, and medical history).	X	
6. Subject does not plan to quit smoking within the next three months.	X	X

a. Users of other TNP in addition to CIG smoking may be enrolled into the study if they agree to limit themselves to stick use/CIG smoking (according to their randomization) during the Exposure period

5.1.2 Exclusion Criteria

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

Exclusion Criteria	Screening	Day -2
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).	X	
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., in emergency situations, under guardianship, prisoners).	X	
3. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or any other medical condition (including safety laboratory), which as per the judgment of the Investigator would jeopardize the safety of the subject.	X	
4. Subject experienced within 30 days prior to screening/admission a body temperature >37.5°C or an acute illness (e.g., upper respiratory-tract infection, viral infection, etc.) or the subject has a confirmed or suspected active COVID-19 infection (based on the signs and symptoms observed at the time of assessment)	X	X
5. As per the Investigator's judgment, the subject has medical conditions which do or will require a medical intervention (e.g., start of treatment, surgery, hospitalization) during the study participation, which may interfere with the study participation and/or study results.	X	
6. Subject has relevant history of, or current asthma condition or COPD condition, and/or clinically significant findings.	X	
7. Subject has donated blood or received whole blood or blood products within 3 months.	X	
8. BMI < 18.5 kg/m^2 or ≥ 32.0 kg/m^2.	X	
9. Positive serology test for HIV 1/2, HBV, or HCV [a].	X	

10. Subject has a positive alcohol breath test and/or has a history of alcohol disorder that could interfere with their participation in the study.	X	
11. The subject has a positive urine drug test.	X	
12. Subject or one of their family members[b] is a current or former employee of the tobacco or e-cigarette industry.	X	
13. Subject or one of their family members[b] is an employee of the investigational site or of any other parties involved in the study.	X	
14. Subject has participated in another clinical study within 3 months.	X	
15. Subject has been previously screened or enrolled in this study.	X	
16. Subject is pregnant (does not have negative pregnancy tests at screening and at admission) or is breastfeeding.	X	X
17. For women of childbearing potential only[c]: subject does not agree to use an acceptable method of effective contraception[d].	X	

a. Human immunodeficiency virus, hepatitis B virus, hepatitis C virus

b. As defined by FDA guidance on Human Subject Protection (21 CFR 50.3(l), (m), 50.24(a)(6), (a)(7)(v), b)): "Family member" means among other things "parent", "spouse", "brothers, sisters, and spouses of brothers and sisters" and "any individual related by affinity…whose close association with the subject is equivalent of a family relationship"

c. Women who are not of childbearing potential meet at least one of the following criteria:
- Have undergone hysterectomy or bilateral tubal ligation,
- Have medically confirmed ovarian failure, or
- Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

d. Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety follow-up period.

5.2 Discontinuation of Subjects from the Study

Discontinued subjects (i.e., enrolled subjects that do not complete the study) will include both subjects who withdraw from the study (subject's decision) or subjects who are discontinued from the study by the decision of the Investigator.

Subjects will be informed that they are free to withdraw from the study at any time. Subjects should be questioned for the reason of withdrawal from the study, although they are not obliged to disclose it.

If the subject withdraws from the study, this information will be fully documented by the PI or designee including:

- The early termination procedures for safety assessments will be performed as defined in section 9.6, unless the subject refuses to perform the assessments.
- The samples collected up to the time of withdrawal that have been analyzed and data collected up to the time of withdrawal will be used in the analysis and report. If the subject refuses that non-analyzed samples and data will be used, he/she needs to document his/her disagreement in writing.

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

- Withdrawal of informed consent
- Non-adherence to allocated product
- Subject becomes an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent, sibling, and child)
- Any AE or condition (including clinically significant changes in a laboratory parameter) which at the discretion of the Investigator no longer justifies the subject's participation in this study
- Positive pregnancy test
- Discontinuation considered to be in the best interest of the subject or the other subjects, as judged by the Investigator
- Subject unwilling to use the product during the entire study duration after having done the product test
- An alternate subject that has completed the 28-day Screening period and has not been randomized
- The Sponsor terminates the study, or the study terminates at a particular site. If the Sponsor decides to prematurely terminate the study, the subjects will be promptly informed. The Investigator or designee should report the fact and the reason in writing to the IEC
- The Investigator terminates the study or suspends the trial (e.g., due to a loss of key staff members, change of circumstances). If the Investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator must inform the institution as applicable, and must promptly inform in the sponsor and the IEC in writing, including a detailed explanation.

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

- Non-compliance to the study procedures based on the judgment of the Investigator
- Violation of eligibility criteria

Subjects who will be discontinued from the study before enrolment will be replaced. After enrolment but before randomization, subjects who will be discontinued from the study will enter the 3-day Safety follow-up period and will be replaced (except alternate subjects). In general, subjects that are discontinued after randomization will not be replaced. Should there be the need to discontinue all subjects from one cohort, e.g., all subjects suspected to have contracted a disease pathogen, subjects for a replacement cohort may be enrolled and randomized.

5.3 Lost to Follow-up

A reasonable attempt will be made to contact all participants needing to complete or resolve post-study activities (e.g., safety laboratory, physical examination, on-going AEs). Two contacts will be made via contact information provided by the subject (e.g., telephone number, cell phone number, email address), allowing 1 day between attempts for response.

If contact is not possible, a follow-up letter will be sent to the participant, allowing approximately 5 business days from the time of delivery for a response. A progress note will be added in the data collection system for documentation. After a letter is sent, there should be no additional phone calls unless the participant has attempted to contact the investigational site and a return call attempt is made.

If post-study follow-up has not been resolved within approximately five business days following delivery confirmation or the letter is not deliverable, the participant is considered lost to follow-up. This is documented in the progress note and outstanding AEs are updated. The date of lost to follow-up corresponds to the date of the end of study of the subject.

The Investigator or designee(s) will declare the subject lost to follow-up if the investigational site lost contact to the subject and the subject has reached the maximum number of study days (39 days) without making any contact.

5.4 Violation of Selection Criteria

Detected violations of eligibility criteria post enrollment may require subjects to be discontinued from the study based on a case-by-case decision of the Investigator.

6 Investigational Products

6.1 Description of Investigational Products

The distribution, dispensation and return of investigational products will be controlled by qualified and appropriately trained investigational site staff.

6.1.1 Investigational Product: Tobacco Heating Systems

The products tested in this study are the THS Blade device (with corresponding Blade Regular sticks) and the THS Induction Mono device and Induction Mid device (with corresponding Induction Regular sticks). Blade sticks are incompatible with the Induction devices, and vice versa.

The THS devices and one variant of the sticks (Regular, i.e., tobacco flavor) will be supplied by the Sponsor.

The THS devices provided by the Sponsor comprise the following components:

- THS Blade device: Charger, Holder, power supply/charging cable
- THS Induction Mono device: Combined Charger-Holder, power supply/charging cable
- THS Induction Mid device: Charger, Holder, power supply/charging cable.

6.1.2 Investigational Product / Baseline Product: Cigarettes

Subject's preferred brand of commercially available regular CIG will not be provided by the Sponsor.

All eligible subjects will be asked to purchase their usual brand of CIG prior to Admission (Day -2). Every subject will bring a sufficient number of unopened, single-brand packs of CIG for the entire confinement period which will be kept in secured storage room at site with access limited to authorized personnel.

6.1.3 Packaging and Labelling

At Admission (Day -2), all study subjects will provide sealed packs of CIG (sufficient for the confinement period) to the investigational site staff. The CIG packs provided by the subject should not be opened and the cellophane cover should be intact.

Each pack of CIG provided by the subject will be labeled to identify to which subject the CIG belong to. The investigational site staff will return all unused products to the subjects at Discharge or Early termination.

For THS, packs of Blade Regular sticks and Induction Regular sticks will be printed with the necessary information including, but not limited to, product code, expiry date, and notification of limiting THS Devices and sticks to investigational use only.

6.2 Use of Investigational Product(s)

Subjects will not be forced to smoke CIG or use THS Regular sticks or Induction Regular sticks, respectively, and will be free to stop smoking/using THS at any time of the study.

During the Screening period, subjects will be allowed to smoke and use TNP according to their product use habits except during the procedures of the Screening visit (section 9.1).

6.2.1 Admission Day (Day -2 to Day -1)

Subjects will be informed on the use of THS and will perform a product test with THS Blade device and THS Induction Mono device with at most three sticks per THS device. CIG smoking will be allowed *ad libitum* from the time of admission of the subject until approximately 11:00 PM, except before and during assessments requiring smoking breaks. Use of any TNP other than CIG and THS will not be allowed after admission.

6.2.2 Baseline Period (Day -2 to Day -1)

All subjects may continue smoking their CIG *ad libitum,* except before/during assessments requiring smoking breaks.

6.2.3 Exposure Period (Day 1 to Day 5)

Except during study procedures, subjects can use THS or consume CIG as per assigned study arm. Site staff will distribute assigned investigational products to the subjects and record all products distributed in the source documentation. Use of any TNP other than the assigned investigational product will not be allowed. The exposure period to the assigned investigational product (IP) will end at Day 5, 11:00 PM, after which subjects will be asked to remain abstinent of any use of TNP until the end of their 24-hour urine collection and completion of study procedures on Day 6.

6.2.4 Day of Discharge (Day 6)

Subjects may smoke CIG or use other TNP at their discretion after Discharge.

6.2.5 Safety Follow-up Period

Following the discharge on Day 6 (or Early termination or discontinuation) and during the subsequent 3-day Safety follow-up period, subjects will be free to use any TNP according to their usual habits.

6.2.6 Stopping Rules for Investigational Product

For safety purposes, using THS or smoking CIG should be temporarily stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach pains, or abdominal pain), cold sweats, headache, dizziness, or breathing problems, or any reasons at the discretion of the Investigator.

For subjects who are discontinued, the reason for discontinuation should be documented in the source documents and in the CRF and subjects will undertake early termination procedures (section 9.6), unless they disagree, or certain procedures have already been performed.

6.3 Method for Assigning Subjects to Study Arms

At the end of the Baseline period enrolled subjects will be randomized using an interactive web and voice response system (IxRS) on Day -1 at any time during the day. Subjects will be informed of their randomized study arm in the morning of Day 1, prior to 06:30 AM (the start of the Exposure period). Subjects will be randomized (stratified by sex) to one of the four study arms (THS Blade device, THS Induction Mono device, THS Induction Mid device, or CIG) in a 1:1:1:1 ratio.

Quotas will be applied to ensure that the randomized population contains at least 40% of both sexes (males and females) overall.

Any alternate subject that has not been randomized will enter the 3-day Safety follow-up period.

6.4 Blinding

This is an open-label study; hence the subjects and Investigator(s) will be unblinded to the subject's arm.

6.5 Investigational Product Accountability and Adherence

6.5.1 Dispensing Investigational Products

CIG for consumption during the confinement period, i.e., on Day -1, and in the CIG arm until end of Exposure period on Day 5 11:00 PM, will be dispensed by the investigational site staff as per the study design.

THS Blade device, Induction Mono device, or Induction Mid device, and corresponding sticks (Blade Regular, Induction Regular) will be dispensed by the investigational site staff for use at the product test on Admission Day -2, and from Day 1 onwards until the end of Exposure period on Day 5 11:00 PM in the corresponding THS arms.

On each day of the confinement period, the time of dispense and return for each product (CIG/sticks) use will be documented for Day -1, and from Day 1 until end of Exposure period on Day 5 11:00 PM.

6.5.2 Storage and Accountability

The sticks (Blade Regular, Induction Regular) and CIG will be stored in a secured storage location at site with access limited to authorized personnel only. The study collaborator designated by the PI will be responsible for the storage and accountability of the IPs in accordance with Sponsor's requirements. Sticks must be stored under controlled conditions (temperature ≥+5° Celsius, ≤+30° Celsius; relative humidity ≤60%), whereas CIG can be stored in normal conditions (at ambient temperature with no temperature and humidity control).

During the confinement period, subjects will return each used stick or CIG butt immediately after smoking to the site collaborators for accountability. The time of return of the products will be documented in an appropriate log.

6.5.3 Investigational Product Retention

Used and unused THS devices and sticks will be returned to the Sponsor or disposed as per Sponsor's instructions upon study completion. Smoked CIG butts will be disposed upon study completion once accountability is completed adequately.

6.5.4 Adherence to Investigational Products

During the confinement and particularly the Exposure period, adherence will be ensured by strict distribution and collection of any used and unused sticks (and corresponding THS) and CIG/CIG butts by designated investigational site staff. Distribution and return of these products will be documented in appropriate logs.

6.6 Restrictions

6.6.1 Smoking Restrictions

During the Screening period, subjects will be allowed to use any TNP according to their usual habits except during the procedures of the Screening visit (section 9.1.1). Spirometry assessments at Screening visit and at Day -1 will be performed at least 1 hour after stopping smoking (section 9.1.1 and 9.2.2).

From Admission (Day -2) to Discharge (Day 6) or Early termination, use of any TNP, except use of the allocated investigational products, will not be permitted.

To avoid cross smoke contamination between the four study arms during confinement period, subjects must use their assigned product (THS or CIG) in separate smoking rooms.

Using THS or smoking CIG will not be allowed during study procedures.

6.6.2 Dietary Restrictions

A standard diet will be designed by a dietician for the whole confinement period. For each meal, the caloric and fat content should be controlled to avoid a "high-fat" diet. A "high-fat" diet is defined as a diet which contains "approximately 50 percent of total caloric content of the meal [from fat] and is high in calories (approx. 800 to 1000 calories)" [17].

To avoid any effect on assessment of BoExp, grilled or pan-fried meat, pre-cooked meats (e.g., tuna, ham, corned beef, and smoked meats), bacon and sausage will not be permitted. In addition, alcohol, broccoli, brussels sprouts, cauliflower, grapefruit and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana, etc.) will not be allowed.

Subjects will not be allowed to bring their own food (including sweets or chewing gum, etc.) or beverages to the investigational site. Meals will be served according to the agreed schedules. Additional light snacks, fruits (except grapefruits), and raw vegetables can be distributed to the subjects without restrictions at any time during confinement if they comply with the dietician's standard diet. Consumption of non-carbonated water is allowed. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the study. The same menu and meal schedule will be administered uniformly for all subjects in all study arms.

A fasting state will be observed for at least 6 hours prior to blood drawings for safety laboratory panel on Day -1 and Day 6.

6.7 Concomitant Medication

All medication taken within four weeks prior to the ICF signature will be considered prior medication. All medication taken from Screening visit to end of the Safety follow-up period will be considered Concomitant medication.

Medications will be allowed and carefully monitored during the study by the Investigator or designee. The Investigator(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 medication will be taken in the best interest of the subject. The use of any concomitant medication must be fully documented in the source document and transcribed into the CRF.

7 Study Procedures

Personnel performing study assessments must have the appropriate and fully documented training. An overview of all study assessments is shown in the schedule of events (see Appendix A). In this section, only the expected/planned timepoints for the various assessments are described. 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

Prior to any study assessment being performed, the subject will be asked to provide his/her written consent to participate to the study (ICF for study participation) (section 9.1.1). All the assessments must start after the time of ICF signature by the subject for study participation.

In addition to the consent for study participation, the subject will be asked to provide her/his optional consent for biobanking (see section 1.3.1). The subject's participation in the study does not depend on the optional ICF.

All consents will be captured in the eCRF.

7.2 Information on Smoking Risks, Smoking Cessation Advice, and THS Briefing

Each subject will be given during the same session i) information on the risks of smoking, ii) smoking cessation advice, and iii) briefing on THS as per schedule of events (see Appendix A).

The information on the risk of smoking and the advice on smoking cessation will take the form of a brief interview according to the WHO recommendations and of the Public Health Service [18, 19]. The briefing of subjects on THS will address any intended or unintended beliefs that participants may have about THS. The goal of the briefing is to help ensure that subjects enter and exit the study with an accurate understanding of the product risks, including an understanding that THS have not been demonstrated to be less harmful than CIG.

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 Investigator(s) and may additionally be given in a group session.

7.3 Clinical and Other Assessments

The results of the clinical assessments described in this section will be recorded in the CRF.

Any clinically relevant medical condition detected during Screening visit assessments has to be documented as a concomitant disease. This also applies to clinically relevant findings in laboratory values, vital signs, spirometry, and ECGs detected during Screening visit assessments. Any untoward medical occurrence in a subject detected during the study, which was not present at Screening visit must be documented as an AE. Worsening of a pre-existing condition from Screening visit onwards will also be documented as an AE.

7.3.1 Demographic Data

Sex, year of birth, and race will be recorded.

7.3.2 Medical History, Concomitant Disease, Previous and Concomitant Medications

Relevant medical history or any concomitant disease will be documented at the Screening visit. Medical history is defined as any condition that started and ended prior to the ICF signature at the Screening visit. A concomitant disease is defined as any condition that is either detected or is still ongoing at the time of ICF signature. The final status of any concomitant disease (i.e., stop date or ongoing) should be verified at each visit.

Prior medication taken within four weeks prior to the Screening visit and any concomitant medication will be documented. Any medication started prior to the Screening visit and still being taken by the subject will be considered concomitant medication. Medication initiated after the Screening visit will also be referred to as concomitant medication. The definition of concomitant medication applies to both prescribed and over-the-counter products.

Records of medication taken should include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), dose and frequency (expressed in metric units, for example, mg, mL, or IU [international units]), indication, and the start and, if applicable, the stop date (day, month, and year). Therapy changes (including changes of regimen) during the study will be documented. If a concomitant medication is still being taken by the subject at the end of the study, this will be recorded in the CRF.

7.3.3 Physical Examination

A physical examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, thyroid gland, chest, lungs, back, abdomen, dentition, gastrointestinal, cardiovascular, musculoskeletal and neurological systems. The physical examination is to be conducted by the Investigator or designated fully trained representative.

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

7.3.4 Body Height and Weight

Body weight and height will be recorded at the Screening visit, body weight will also be recorded at Admission Visit Day -2.

The BMI will be calculated from the body weight and height using the following formula:

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

The BMI will be used to assess eligibility for enrolment.

7.3.5 Vital Signs

Vital signs will include systolic and diastolic blood pressure (BP), respiratory rate (RR) and heart rate (HR).

All parameters will be recorded in supine position after the subject has rested for at least 5 minutes. Subjects should have abstained from using any TNP for at least 15 minutes prior to Vital signs assessment.

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

7.3.6 Spirometry

Spirometry will be performed in accordance with the 2019 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry [20, 21]. Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set [22].

Assessed parameters will include: FEV_1, FEV_1 % predicted, FVC, FVC % predicted and FEV_1/FVC.

All personnel performing spirometry testing should have the appropriate training and quality control measures should be put into place and be properly documented. The testing will be performed in sitting position at rest for at least 15 minutes and at least 1 hour after smoking CIG (Screening visit).

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

Any printouts of Spirometry on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents.

7.3.7 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

All ECGs will be reviewed on an ongoing basis by the Investigator or designee. The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected according to Fridericia's formula.

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

Any printouts of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents

7.3.8 Biomarker Assessments

All bioanalytical assays and laboratory assessments will be carried out using validated methods. The bioanalytical methods used will be documented in the respective bioanalytical plans/reports. A list of laboratories is provided in Appendix B.

Blood samples and 24-hours urine samples will be collected according to the schedule of events (Appendix A) to measure BoExp to nicotine and some HPHC:

- In blood: carboxyhemoglobin (% of saturation of hemoglobin)
- In 24-hours urine: 3-HPMA, 2CyEMA, MHBMA, total NNAL, S-PMA, 2-HEMA, 3-HMPMA, total NNN, 3-OH-B[a]P, 4-ABP, and 2-NA (creatinine normalization).

7.3.9 Laboratory Assessments

Subjects should have fasted for at least 6 hours prior to hematology and clinical chemistry analyses, except at Screening visit and Early Termination where non-fasting samples can be used. Tests will be conducted at a local laboratory (see Appendix B). If during the screening period a blood sample is not suitable for analysis (e.g., blood clotting) a re-test should be performed for the specific parameters which are not available. Safety urine analysis will be also assessed.

Parameters to be tested are listed in Appendix C.

Serology

At the Screening visit, tests for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus will be performed.

Urine Drug Screening

The urine will be screened for amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and methadone.

In case of a positive urine drug test, a re-test will not be allowed to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test.

Urine Cotinine Screening

A urine cotinine test will be performed to confirm the nicotine/tobacco use status.

The test must detect cotinine with a threshold of ≥ 200 ng/mL. In case of a negative cotinine test, a re-test will not be allowed to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test.

Alcohol Test

An alcohol breath test will be performed at Screening visit.

Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects of childbearing potential. Subjects with a positive pregnancy test or unclear results (from two repetitions) before product testing and enrolment will be considered as screen failures. In case of any positive pregnancy test, the Investigator or designee will inform the subject about the risks associated with smoking during pregnancy and subjects will be referred to health care facility/health care provider for pregnancy follow-up.

All pregnancies detected during the study must be reported and handled as described in section 8.5.

7.3.10 Sample Handling, Storage, and Shipment

Urine drug test, urine pregnancy tests, and urine cotinine test, as well as all safety panel tests, will be done by the site personnel at the site. All other blood and urine samples will

be managed by the laboratory designated in Appendix B. Detailed procedures for handling of samples will be described in the Laboratory Manual/Sample Handling Manual (LM/SHM). Safety laboratory samples will be destroyed as per laboratory local regulations. All other samples (except biobanking samples) will be destroyed after the Clinical Study Report (CSR) has been finalized. The facilities at which the samples are stored will request confirmation in writing by the Sponsor when destruction of the samples shall be performed.

Blood Samples

Blood samples will be drawn by qualified and trained site personnel and according to the standard operating procedures (SOPs) at the investigational site.

Since the test for nicotine concentration is highly sensitive, precautions should be taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine.

In total, approximately 95 mL of blood will be collected for this study including samples for determination of serology (5 mL), COHb (30 mL) and safety laboratory (approximately 60 mL). This calculation is based on an individual volume of each sample of 20 mL per safety laboratory assessments, 5 mL for serology, and 5 mL for COHb assessment. The total volume of blood drawn (approximately 95 mL) will not exceed the levels for a standard blood donation.

Details on the procedures for collection, labelling, processing, and shipment of samples will be described in the LM/SHM.

Urine Samples

Spot urine samples will be used for the urine drug screen, urine cotinine screen, urine pregnancy test, and safety urine analysis at Screening visit, Admission visit on Day -2, and after completion of 24-hour urine sample collection on Day 6.

24-hour urine collection Subjects will discard their first void in the morning of Day -1. 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 in 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 aliquots from the 24-hour urine collection will be taken. In the schedule of events for the 24-hour urine collection, the dot corresponds to the day on which the 24-hour urine collection period starts.

Biobanking of urine If a subject gives optional consent for biobanking, additional samples of urine from the 24-hour collection will be aliquoted. The samples intended for biobanking will be kept frozen and will be shipped to a central storage facility according to the LM/SHM. After the final CSR is signed, samples of urine will be stored for a maximum duration of 2 years.

7.4 Other Study Procedures

7.4.1 Demonstration of THS and Product Test

All subjects will have a demonstration of THS by the investigational site staff at the Screening visit without product use.

At Admission (Day -2), after enrollment, investigational site staff will inform subjects on product use and subjects will have a product test with THS Blade device and Induction Mono device with up to three sticks per THS for a duration of approximately one hour.

7.5 Questionnaires

The study questionnaires will be completed by the subjects in a paper format. All subject-reported measures as well as instructions will be provided in the subject's local language.

7.5.1 Tobacco/Nicotine Product Use History

Subjects will be asked questions about their TNP use history. The questions will capture frequency and quantity of TNP use over the past four weeks, the flavor of cigarettes the subjects do smoke, the number of continuous years of CIG smoking, the duration of cessation attempts over the past three years, and the intention to quit smoking within the next 3 months. This information will be used as characteristics of the study subjects, to assess their eligibility to participate in the study, and to serve as baseline values.

7.5.2 Fagerström Test for Nicotine Dependence (Revised Version)

Self-reported level of nicotine dependence will be assessed via a questionnaire on Baseline Day -1 using the Fagerström Test for Nicotine Dependence (FTND) in its revised version [23], as updated in 2012 [14]. The questionnaire consists of six questions which will be answered by the subjects. 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) [23]. This information will be used as characteristics of the study subjects.

7.5.3 ABOUT–Product Experience Questionnaire

Product experience will be assessed via the ABOUT–Product Experience, a subject self-reported outcome measure part of the ABOUT toolbox [24].

The questionnaire consists of 3 multi-item scales and 2 single-item scales, arising from an adaptation and rewording of the modified cigarette evaluation questionnaire (mCEQ) [15] to RRPs and the Product Evaluation Scale [25].

The questionnaire assesses the perceived effects experienced by CIG smokers switching to THS Blade device, Induction Mono device, or Induction Mid device compared to the experience of subjects continuing CIG smoking by measuring:

- Product satisfaction (satisfying, tastes good, enjoy the product).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nausea).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

Subjects will be asked to assess the items of the questionnaire on a 7-point scale, ranging from “not at all” to “extremely”. A score for each subscale will be computed based on the scoring rule established by the questionnaire developer [15].

Symptoms or worsening of symptoms documented in the questionnaire do not need to be documented as additional AEs as the main source for AE collection is the face-to-face interview between the subject and study site staff, using open, non-directive questions, as described in section 8.2.1.

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) is defined as any health-related event which is adverse or unfavorable and which either starts after ICF signature or represents a worsening of a health–related condition that existed at the time of that signature. Careful medical judgment is required to establish whether a clinical finding (including an abnormal laboratory result) is a true AE or just a manifestation of a preexisting health–related condition. An AE may or may not have a causal relationship with the study procedures or with the use of investigational product.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate Investigator's 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.

"Life-threatening" means that the subject was at immediate risk of death from the event. It might have caused death if it had occurred in a more serious form.

8.1.3 Conditions Existent Before the Start of the Period of Collection (ICF signature)

Concomitant diseases whose severity is increasing after the Screening visit are to be captured as AE or SAE, depending on if any seriousness criterion is met.

Therapies or surgical interventions including admissions to hospital that had been planned before the ICF signature should not be considered AEs/SAEs.

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Information

AEs should be collected mainly via face-to-face interview with the subject by the use of consistent, open, non-directive questions from the investigator(s) or designee(s) (e.g., "How have you been feeling since you were last asked?").

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE CRF, and on the SAE form for recording into safety database.

Information recorded for AEs/SAEs will include verbatim description, start and stop dates, seriousness, severity (intensity), causal relationship with IP and study procedures, action taken with IP (e.g., reduced, not changed), other action taken (e.g., treatment administered, if led to the subject's discontinuation from the study), and outcome (e.g., resolved, stabilized).

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms.

8.2.2 Period of Collection

AEs (including SAEs) will be collected from the time of ICF signature until the individual EOS for each participant.

Any AEs which occur during the Screening period will be captured by the investigational site staff and assessed by the Investigator or designee(s) to establish relationship to study procedures.

During a 3-day Safety follow-up period new AEs/SAEs will be recorded and ongoing AEs/SAEs will be followed-up by the study site, as described in section 8.2.6.

8.2.3 Intensity of Adverse Event

The Investigator must assess the intensity of each reported AE according to the following grading scale:

Table 5 Intensity of Adverse Events

Mild:	Easily tolerated, not interfering with normal everyday activities

Moderate:	Interferes with normal everyday activities, but the subject is still able to function
Severe:	Incapacitating and requiring medical intervention

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

The Investigator must assess the causal relationship between the exposure to the IP (THS or CIG) and each of the reported AEs, using the classification system and the criteria described below. The same assessment must be made separately to assess the causal relationship between the study procedures and each of the reported AEs:

Not related: The temporal relationship of the adverse event to IP administration or study procedure(s) 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 adverse event to IP or study procedure(s) 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 (THS or CIG) will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with information already recorded in section 6.7 of the current Investigator's Brochure [6].

8.2.6 Follow-up of Non-serious and Serious Adverse Events

Any non-serious AE that is ongoing at the time of Discharge or early termination will be followed-up by the Investigator during the Safety Follow-Up Period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). The follow-up of the ongoing non-serious AEs will be done via a phone call performed at the end of the Safety Follow-Up Period. If the subject is not responding at the first phone call, two additional attempts will be made, then subject will be declared lost to follow-up.

At the end of the 3-day Safety Follow-Up Period, all ongoing non-serious AEs will have the outcome documented as "unknown" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner to have his/her ongoing AEs addressed accordingly.

All SAEs will be followed up by the Investigator or designee after the end of the Safety Follow-Up Period, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). In case the subject cannot be reached for additional information related to SAE(s), a total 3 attempts should be performed before the subject will be declared as lost to follow-up.

8.3 Reporting Serious Adverse Events

Any SAE observed during the period of collection in this study must be reported **within 24 hours of first awareness to Sponsor**, via email, having the SAE form attached.

Follow-up information should be reported on a new SAE report form, marked as a follow-up report and submitted to Sponsor according to the same timelines as described above. The follow-up SAE report form must include the minimum information required 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.

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the IEC, according to local regulations.

8.4 Reporting of Other Abnormal Findings

The other abnormal findings discovered during different clinical assessments (e.g., ECG, spirometry, vital signs, body weight) should be evaluated for the clinical significance by the Investigator/designee based on his/her medical judgement. All abnormal clinically significant test results or clinical examination findings can, at the discretion of the Investigator, be reported as AEs and handled according to the directions from section 8.2.

8.5 Reporting and Follow-Up of Pregnancies

8.5.1 Period of Collection and Follow-up

Pregnancies detected between the time of signature of the ICF and the time before first exposure to the IP will be considered a reason for screen failure. No pregnancy form will be filled in for that case, however the diagnosed pregnancy must be captured in the screen failure page of the CRF.

Any pregnancy detected after enrollment must be reported by the Investigator within 24 hours. This also includes pregnancies spontaneously reported to the Investigator after the end of the study for a subject. A dedicated pregnancy form will be used to report reportable cases of pregnancy.

Any pregnancy that was potentially associated with exposure to IP (THS and CIG) will be followed-up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination), and until 8 weeks after delivery. Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded as an AE accordingly.

The procedure outlined in Section 8.3 should be followed to collect pregnancy reports and provide any additional/follow-up information to Sponsor.

8.5.2 Reporting of Pregnancies

The Investigator is responsible for informing the responsible IRB of any pregnancy case that was reported during the study, as determined by local regulations.

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the Early termination (section 9.5), as soon as practical after discontinuation and will enter the 3-day Safety Follow-Up Period.

Any AEs or SAEs that are ongoing at the end of the Safety Follow-Up Period will be managed as described in section 8.2.6.

8.7 Device Malfunction, Product Complaints and Misuse

Any occurrence of investigational product THS device malfunction, product complaints, or misuse (use not in accordance with its instructions) by a subject will be documented by the Investigator. Information regarding the investigational product THS events should be actively collected during the study and assessed for severity as Minor or Major:

Minor – Can be resolved easily.

Major – Cannot be resolved.

Any occurrences of investigational product THS device malfunction (e.g., holder does not charge when inserted into the charger), product complains (e.g., stick filter fall off) or misuse by a subject (use not in accordance with its label and instructions), will be documented by the Investigator or his/her designee using a device issue log.

Investigational product misuse may result in use-related hazards (section 2.2.3).

Furthermore, any malfunction or misuse of the investigational product THS that leads to an AE/SAE will follow the same processes as described above.

9 Study Activities

A detailed schedule of assessments can be found in Appendix A. Measurements not conducted at the exact timepoint but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given timepoint.

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

9.1 Screening Period

9.1.1 Screening Visit (between Day -30 to Day -3)

The Screening visit will be performed ≤28 days prior to enrollment at Admission (Day -2). First, the ICF along with study information will be given to the subject. Prior to being asked to sign the consent form, subjects will be given time to review the study information and ask any questions. When/if the ICF is signed and dated and timed, the screening procedures can be performed in the order deemed most practical. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed at the Screening visit.

Screening activities and examinations are listed in Table 6:

Table 6 Time Schedule – Screening Visit

Time	Procedures	Additional Information
Start of Procedure	**Screening Visit**	
Prior to any other study procedure	Informed consent process and signature of ICF	
During the Visit	Information on smoking risks, advice on smoking cessation	Including THS briefing
	Inclusion/exclusion criteria	
	Smoking history	TNP Use History questionnaire
	ECG	
	Spirometry	
	Demographics	
	Medical History / Concomitant Diseases	
	Prior (≤4 weeks) and concomitant medication	

Time	Procedures	Additional Information
Start of Procedure	**Screening Visit**	
	Physical examination	
	Body height and weight / BMI	
	Vital signs	
	Serology	HBV, HCV, and HIV
	Collection of blood sample	- Safety panel (hematology, clinical chemistry)
	Collection of spot urine	- Safety panel - Drug test - Cotinine test - Pregnancy test (all WOCBP)
	Alcohol breath test	
	Review of eligibility criteria	
	THS demonstration	Without product use
	Identification of current CIG brand	Explain CIG provision for confinement period by subject
	AE/SAE recording	

Abbreviations:

AE = Adverse event; BMI = Body mass index; ECG = electrocardiogram; CIG = regular cigarette; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; SAE = Serious adverse event; THS = tobacco heating system; TNP = tobacco and/or nicotine containing product; WOCBP = women of child-bearing potential.

If the eligibility criteria are met, the site staff will contact the subject to arrange the visit for Admission Day -2 at the site.

9.2 Baseline Period (Enrolment and Randomization)

9.2.1 Admission Day -2

Day -2 should be scheduled within 28 days after Screening visit[1].

Enrollment of a subject will take place at Day -2 only if all eligibility criteria are met, and after confirmation of a negative pregnancy test (women of child-bearing potential [WOCBP] only). The confinement period will start after the successful enrollment. All

[1] Alternate subjects will have to repeat the Admission Day -2 visit to qualify for randomization. The data of that repeated visit will be captured in the database as “Admission Day -2 visit – Second occurrence”.

other procedures (Table 7) and data collection will be completed following the enrollment of the subject.

Table 7 Time Schedule – Admission Day -2

Time	Procedures	Additional Information
Start of Procedure	**Admission Visit Day -2**	
Start of the visit	Check-in at site	CIG use allowed on site on Day -2
Prior enrolment	Collection of spot urine	- Drug test - Cotinine test - Pregnancy test (WOCBP)
	Body weight	BMI calculation
	Vital signs	
	Smoking history	TNP Use History questionnaire
	Inclusion/exclusion criteria	
	Information on smoking risks; advice on smoking cessation	Including THS briefing
Prior to breakfast	Enrollment	After confirmation of the eligibility of the subject
	Start of run-in period	
During the visit	Breakfast	
	Lunch	
	THS product test	Subject can test THS with three sticks per THS
	Concomitant medication	
	Concomitant disease status	
	AE/SAE recording	
	THS product events and complaints	
End of the visit	Subjects remain confined	11:00 PM stop of smoking

Abbreviations:
AE = Adverse event; BMI = Body mass index; CIG = Conventional cigarette(s); FTND = Fagerström test on nicotine dependence; SAE = Serious adverse event; THS = tobacco heating system; TNP = tobacco and/or nicotine containing product(s); WOCBP = women of child-bearing potential.

9.2.2 Baseline Visit Day -1

Baseline exams will be performed (Table 8), and subjects will be randomized at Baseline visit. Randomization will take place only for subjects who are willing to comply with study

procedures and to use THS for at least 5 days. Table 8 shows the assessments that will be performed at Baseline Visit Day -1.

Table 8 Time Schedule – Baseline Visit Day -1

Time	Procedures	Additional Information
Start of Procedure	**Baseline Visit Day -1**	
Prior to breakfast	Spirometry	
	ECG	
	Vital signs	
	Collection of blood sample	After ≥6 hours of fasting - Safety panel
	Collection of spot urine	- Safety panel
	Start 24-hour urine collection	For Day -1
	COHb in blood	
Prior to randomization	Breakfast	
During the visit	Randomization	Per IxRS
	FTND	Questionnaire
	Concomitant medication	
	Concomitant disease status	
	AE/SAE recording	
	ABOUT–Product Experience	Questionnaire
	Collection of CIG butts	Accountability
End of visit (11:00 PM)	CIG *ad libitum* consumption stop	Subject remains confined

Abbreviations:
ABOUT = Assessment of Behavioral OUtcomes related to Tobacco and Nicotine Products; AE = Adverse event; COHb = Carboxyhemoglobin; CIG = Conventional cigarette(s); FTND = Fagerström Test for Nicotine Dependence; IxRS = Interactive voice/web response system; SAE = Serious adverse event.

9.3 Randomized Exposure Period

9.3.1 Exposure in Confinement Period

On Day 1, subjects will be informed about their allocation to a study arm, i.e., either THS Blade device, Induction Mono device, Induction Mono device, or CIG. Table 9 shows the assessments that will be performed at Day 1, 2, 3, 4, and 5.

Table 9 Time Schedule – Day 1, 2, 3, 4, and 5

Time	Procedures	Additional Information
Start of Procedure	**Day 1, 2, 3, 4, and 5**	

Prior to breakfast	Vital signs	
	COHb in blood	
	Completion of former day urine collection	Each day of the confinement period
	Start of next 24-hour urine collection	Day 5 collection will be completed in the morning of Day 6, ahead of Discharge
	Day 1 only: Inform subjects on allocated study arm	
During the visit	Breakfast	
	Distribution of the THS	Subjects in THS arms
	Provision of single sticks	Subjects in THS arms
	Provision of single CIG	Subjects in CIG arm
	Collection of sticks	Subjects in THS arms
	Collection of CIG butts	Subjects in CIG arms
	Concomitant Medication	
	Concomitant Diseases	
	AE/SAE recording	
	ABOUT–Product Experience	Questionnaire
	THS product events and complaints	THS arms only
End of visit (11:00 PM)		Subjects remain confined

Abbreviations:
ABOUT = Assessment of Behavioral OUtcomes related to Tobacco and Nicotine Products; AE = Adverse event; COHb = Carboxyhemoglobin; CIG = Conventional cigarette(s); SAE = Serious adverse event; THS = tobacco heating system.

9.4 Discharge

At Day 6, following completion of the procedures and examinations (Table 10), the subjects will be discharged for the Safety follow-up period.

Table 10 Time Schedule – Discharge Day 6

Time	Procedures	Additional Information
Start of Procedure	**Day 6**	
Prior to breakfast	Collection of blood sample	After ≥6 hours of fasting - Safety panel
	Completion of Day 5 urine collection	
	Collection of spot urine	- Safety panel - Pregnancy test (WOCBP only)
	Vital signs	
	Spirometry	
	ECG	
During the visit	Breakfast	
	Concomitant medication	
	Concomitant diseases	
	AE/SAE recording	
	THS product events and complaints	THS arms only
	Information on smoking risk; smoking cessation advice; and briefing on THS	
End of the visit	Discharge from site	

Abbreviations:
AE = Adverse event; ECG = Electrocardiogram; SAE = Serious adverse event; THS = tobacco heating system; WOCBP = women of child-bearing potential.

9.5 Safety Follow-up Period

After Discharge at Day 6, the subjects will enter a 3-day Safety Follow-Up Period during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted by the study investigational site as described in section 8.2.6.

9.6 Early Termination Procedures

When a subject is discontinued from the study, all Early termination procedures listed in Table 11 are performed unless the subject refuses to perform the assessments or the procedures have already been performed during that study day.

Table 11 Time Schedule – Early Termination Visit

Procedures	Additional Information
Collection of blood sample	After ≥6 hours of fasting, if possible - Safety panel
Collection of spot urine	- Safety panel - Pregnancy test (WOCBP only)
Vital signs	
ECG	
Spirometry	
Information on smoking risks; advice on smoking cessation; and briefing on THS	
Concomitant medication	
Concomitant diseases	
AE/SAE recording	
THS product events and complaints	THS arms only
Discharge	

Abbreviations:

AE = Adverse event; ECG = Electrocardiogram; SAE = Serious adverse event; THS = tobacco heating system; WOCBP = women of child-bearing potential

10 Quality 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 Investigator(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 Investigator(s) shall provide access to medical records for the Monitor in order that entries in the CRFs may be verified. As part of his/her(their) responsibilities, the Investigator(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.

Subsequently 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. The monitoring is performed using a risk-based approach as described in the monitoring plan (please refer to section 10.4 describing overall study risk management).

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 Investigator(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 meeting) may 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 Investigator(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 Investigator(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 IEC 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 Investigator(s) will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.

The Investigator(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 Investigator(s) understand(s) and agree(s) to provide access to the necessary documentation and files.

10.4 Risk Management

According to ICH-GCP E6(R2) Section 5, the sponsor will implement a system to manage quality throughout all stages of the study process. Pursuant to this, a risk management process will be implemented including identification and scoring of risks, identification of critical data and processes as well as the definition of Key Risk Indicators (KRI) and Quality Tolerance Levels (QTL).

This risk management approach will be captured in a Risk Management Plan/Report with risks assessed in the Risk Management Tool which will be used during the set-up phase of the study and reviewed throughout all stages of the study.

In addition, at the end of study, the sponsor will describe the quality management approach implemented in the study and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the CSR.

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, eCRF and EDC (electronic data capture) will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

Electronic Case Report Forms (eCRFs) are produced by the CRO responsible for Data Management activities (DM-CRO), stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between DM-CRO and the Sponsor (e.g., CD, flash drive, SFTP). This will be documented in the DMP. The subject questionnaires will be completed directly by the subject on paper and transcribed by the site personnel to eEDC. 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 to transfer the data into the eCRF, in accordance with the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The eCRF must be signed by the Investigator to attest that the data contained in the eCRF are true and accurate. Any correction made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. The eCRF for each subject will be checked against the source documents at the investigational site by the Monitor. Instances of missing or unclear data will be discussed with the Investigator for resolution. An eCRF will be generated for all subjects that sign the ICF.

11.1.2 Protocol Deviations

Protocol deviations are defined as any departure from the procedures defined in this document, including, but not limited to, any violation of inclusion/exclusion criteria, mis-randomization, use of any nicotine or tobacco-containing product other than the assigned product during the exposure period, assessments not performed or performed outside the scheduled time windows, or use of medications that are known to affect study endpoints.

Protocol deviations will be entered into the clinical trial management system (CTMS) or any other approved format. Protocol deviations will be reconciled and categorized prior to locking the clinical database as described in the DMP.

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

Individual entries for protocol deviations that are recorded in the CTMS, or other approved format, following investigational site monitoring and other manual reviews, will be reviewed against the individual data points in the database. The overall procedure for managing protocol deviations is defined in the SOPs and study specific procedures of the DM-CRO. All deviations will be reviewed, as defined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.1.3 Data Handling

All study data will be managed by the DM-CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the DM-CRO. The DM-CRO will prepare the DMP that will be reviewed and approved by the Sponsor, prior to the start of the study, i.e., First Subject Screened. This document will describe, in detail, the procedures and processes related to data management.

All data of all subjects that are enrolled will be captured and stored in the study database. For screen failures, only the following information should be captured: date/time of ICF signature, year of birth, sex, race, AEs, date, and reason for screen failure.

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

The sponsor should ensure that the Investigator has control of and continuous access to the eCRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

The Investigator should have control of all essential documents and records generated by the Investigator/investigational site before, during and after the study.

Additional details are covered in the DMP.

11.2.1 Data Verification

The data will be verified as defined in the DMP and data validation plan (DVP). Data queries will be raised for discrepant or missing data. All changes to data in the eCRF will be captured in the database with a comprehensive audit trail.

All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

Adverse events, concomitant diseases, medical/surgical history, prior/concomitant medication will be classified according to the terminology of the latest version of the following dictionaries, at time of coding the first entry:

Medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Adverse events / Procedures:	MedDRA®
Medications:	WHO Drug Global

11.2.3 Database Lock

When all outstanding data management issues have been resolved and all validation, quality review and cleaning activities are complete as defined in the DMP, the Sponsor organizes a data review and ensures that the resolution of all raised queries and quality control of the changed data are performed by the CRO before approving the database locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the data management and statistical teams at the CRO. Any changes must be documented in the database log file and if these changes may impact the study analysis the PMP process for a database unlock may be requested.

The study database will be transformed into a Clinical Data Interchange Standards Consortium (CDISC) compliant format and transferred to the Sponsor as specified in the DMP and defined in the data transfer agreement. The clinical data will adhere to the CDISC Study Data Tabulation Model (SDTM) Data Structure Specifications.

12 Planned Statistical Methods

12.1 General Considerations

Full details of the statistical analyses will be described in the Statistical Analysis Plan (SAP). Any changes to the planned statistical methods will be documented in the SAP and clinical study report. The statistical evaluation will be performed using SAS®, version 9.2 or higher.

12.1.1 Stratification Criteria

The following stratification factor at baseline will be used in some of the analyses:

- Sex (male and female).

12.1.2 Definitions for Statistical Data Analysis

The following definition will be used for the statistical analysis of safety data:

Term	Definition
Actual exposure arm	Categorical variable representing the actual study arm of enrolled subjects. Non-randomized subjects will be assigned to the category 'Enrolled but not randomized'. Randomized subjects will be assigned to the category corresponding to their randomization study arm. In case of mis-randomization (use of a different product from the allocated one), subjects will be assigned to the arm corresponding to their actual exposure.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by randomization study arm, subject, and study day 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), 95% confidence interval (CI) of the arithmetic mean, median, first and third quartiles, minimum, maximum; for log-normal data, the geometric mean, geometric coefficient of variation (CV), and 95% CI of the geometric mean will be presented instead of arithmetic mean, SD, and 95% CI of the arithmetic mean, respectively. Post-baseline summaries will include change from baseline apart from log-normal variables which will present % change from baseline.

When applicable, the number and % of subjects with values below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will also be presented.

For categorical data, the number and % of subjects with missing data, frequency counts, and percentages will be presented.

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

Values outside detection limits will be substituted using the following rules (e.g., for BoExp parameters):

- Values below LLOQ will be imputed using LLOQ/2.
- Values above ULOQ will be imputed using ULOQ.

Except otherwise stated, other missing values will not be imputed.

Handling of missing answers to questionnaires will be described in the SAP.

12.2 Product Use

Considering the design of the study, it is expected that, during the exposure period, subjects will only use products corresponding to their randomization arm.

Mis-randomized subjects will be classified according to their actual exposure arm for safety analyses (see section 12.1.2) and excluded from all analyses using the Per Protocol Set (see section 12.3.3).

12.3 Analysis Sets

The following analysis sets will be used for the data analyses.

12.3.1 Screened Population

The Screened Population consists of all subjects who signed the ICF and who underwent at least one of the screening procedures.

12.3.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all the randomized subjects who have at least one post-randomization product use experience (if randomized to CIG or one of the THS arms) and who have at least one valid non-safety assessment after randomization. The FAS will be analysed by randomized study arm.

12.3.3 Per Protocol Set (PP)

The Per Protocol Set (PP) will be a subset of FAS and include all randomized subjects who fulfil key compliance criteria of the protocol, i.e., have no major protocol deviation impacting the evaluability of the primary objective (to be further described in the SAP). The PP will be analysed by randomized study arm.

12.3.4 Safety Set (SAF)

The safety population will consist of all the subjects enrolled in the study with at least one exposure to THS (product test at Admission Day -2), and who have at least 1 valid value for a safety assessment. The SAF will be analyzed according to actual exposure arm (see definition in section 12.1.2).

12.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics include sex, age, race, body weight, height, body mass index (BMI).

Baseline characteristics include TNP use history, spirometry measurements (FEV1, FEV1 % predicted, FVC, FVC % predicted, and FEV1/FVC), and FTND questionnaire score.

Demographics and baseline characteristics will be summarized as follows:

- By randomization study arm for the FAS,
- By randomization study arm for the PP,
- By actual exposure arm for the SAF (see definition in section 12.1.2).

12.5 Primary Objective

The primary objective of the study is to demonstrate the reduction of BoExp to selected HPHC in smokers switching from CIG to each of the THS arms (THS Blade device and THS Induction Mono device and THS Induction Mid device) compared to continuing CIG smoking for 5 days.

12.5.1 Primary Estimand Analysis

The primary estimand of the primary objective is defined by the following components:

- Product Use Under Evaluation: This corresponds to the study arms (CIG, THS Blade device, THS Induction Mono device or THS Induction Mid device) randomly allocated to subjects and for which they have fulfilled key compliance criteria of the protocol without major protocol deviation impacting the evaluability of the primary objective (as defined by the PP).

- Target Population: This is the population of adult smokers who satisfy all eligibility criteria (see section 5.1).

- Variables of Interest: 3-HPMA, 2-CyEMA, total NNAL, MHBMA (all expressed as concentration adjusted for creatinine in 24-hour urine), and COHb (expressed as % of saturation of hemoglobin).

- Intercurrent Events (ICEs):
    - Non-adherences to the randomization study arm: these ICEs are out of scope of this primary estimand, and related subjects will be excluded from this analysis.
    - Study discontinuation and death: data related to subjects who discontinued or died during the exposure period will be included only if they were adherent until the time of discontinuation/death. Missing data after discontinuation/death will be dealt with as described in section 12.5.1.3.
    - Subjects being tested SARS-CoV2 positive during the study: these subjects will be included only until the time of the diagnosis. Data collected after or at the date of the SARS-CoV2 positive test will be set to missing and dealt with as described in section 12.5.1.3.
    - Changes in comorbidities: subjects with comorbidities or worsening of an existing comorbidity will be included as this change may be linked to the reduction or modification of their CIG consumption.
- Population-Level Summary Statistic: geometric mean ratios between every THS arms (THS Blade device, THS Induction Mono device or THS Induction Mid device) and CIG of the BoExp under consideration (Table 3, Table 4) at Day 5.

12.5.1.1 Baseline Comparability

Demographics and baseline characteristics (as described in section 12.4) will be reported by randomization study arm for the PP.

Given that the study is randomized, demographics and baseline characteristics are expected to be balanced between study arms. Nevertheless, sex and baseline value of the BoExp will be used as covariates in the statistical model (see section 12.5.1.4).

12.5.1.2 Descriptive Analysis

Descriptive statistics as mentioned in section 12.1.3 for the variables of interest and associated changes from baseline will be reported by randomization study arm for the PP and by study day. Descriptive statistics stratified by the factor described in section 12.1.1 will also be computed.

12.5.1.3 Missing Data Strategy

In this analysis, some missing data might occur because of ICEs or because of missing samples, laboratory measurements errors, etc. The main analysis model (see section 12.5.1.4) assumes that subjects with missing data would have outcome data like those in similar subjects in the same group. This type of assumption is referred to as Missing at Random (MAR). This assumption is aligned with the definition of the primary estimand.

12.5.1.4 Main Analysis

The primary analysis will be conducted in the PP and based on a mixed model for repeated measurements (MMRM). An unstructured matrix will be used to model the variance-covariance structure within subjects. If this model fails to converge, then the following variance-covariance matrix will be used (in order) until one converges: Heterogeneous Toeplitz, Heterogeneous First Order Autoregressive, Heterogeneous Compound Symmetry, Variance Components, Compound Symmetry, and finally no repeated statement.

The model for the endpoint expressed on the log-scale will adjust for the endpoint value at baseline (log-scale), the Day, the randomization study arm and its interaction with Day, and sex.

The model described above will be implemented in the SAS® language as:

```
PROC MIXED data=dataset method=reml nobound;
    class Arm Day Subject Sex;
    model Log(Endpoint) = Log(Baseline) Day Arm Arm*Day
          Sex / ddfm=kenwardroger2 solution;
    repeated Day / subject=Subject(Arm) type=un rcorr;
    lsmeans Arm*Day / pdiff cl;
    lsmestimate 'Contrast every THS arms (THS Blade Device 1, THS Induction Device 1 or THS
Induction Device 2) vs. CIG' exact syntax to be adjusted depending on the coding of class
variables / cl upper alpha=0.025;
RUN;
```

LS-means per randomization study arm and day will be obtained (on the log-scale), as well as pairwise differences between arms per day, together with their 95%-confidence intervals and (unadjusted) p-values. Exponentiation of these quantities will lead to the geometric LS-means per randomization study arm and (geometric) ratios between arms with their associated 95%-confidence intervals.

The exponentiation of the 'lsmestimate' statement above entitled 'Contrast every THS arms (THS Blade device, THS Induction Mono device, or THS Induction Mid device) vs. CIG' will allow contrasting all THS arms jointly against the CIG arm and will be used to assess the primary study hypothesis (see section 12.5.1.4).

12.5.1.5 Success Criteria

The primary study hypothesis is about demonstrating the reduction of the five BoExp to selected HPHC listed in Table 3 in smokers switching from CIG to each of the THS variants (THS Blade device, or THS Induction Mono device, or THS Induction Mid device, respectively) for 5 days as compared to those who continue smoking CIG. For each individual BoExp, this will be evaluated using the 1-sided statistical test with a type I error level of 2.5% given by the 'lsmestimate' statement 'Contrast every THS arms (THS Blade device, THS Induction Mono device or THS Induction Mid device) vs. CIG' of the model described in section 12.5.1.4.

The study will be declared successful if all ratios of the geometric means between every THS arms (THS Blade device, THS Induction Mono device or THS Induction Mid Device) over CIG is statistically lower than 1 at Day 5 for all five BoExp tested in the primary objective given in Table 3.

12.5.1.6 Supplementary Analysis

The model described in section 12.5.1.4 allows contrasting all randomization study arms at Days 1, 2, 3, 4, and 5. While only the contrast between the three THS arms jointly and CIG at Day 5 will be used for the primary objective assessment, the following pairwise comparisons at Days 1, 2, 3, 4, and 5 will also be reported, together with their unadjusted p-values and 95%-confidence interval:

- THS arms jointly (THS Blade device, THS Induction Mono device or THS Induction Mid device) vs. CIG
- THS Blade device vs. CIG
- THS Induction Mono device vs. CIG
- THS Induction Mid device vs. CIG

12.5.2 Secondary Estimand Analysis

This analysis refers to the secondary estimand of the primary objective defined in section 3.1. This estimand is implementing the "treatment policy strategy" and reflects the intention-to-treat (ITT) principle. It will evaluate the effect of switching to THS as compared to continuing to smoke CIG in the FAS rather than in the PP. It is defined by the following components:

- Product Use Under Evaluation: This corresponds to the study arm (CIG, THS Blade device, THS Induction Mono device or THS Induction Mid device) randomly allocated to subjects and is independent of whether subjects were adherent or not (FAS).

- Target Population: This is the population of adult smokers who satisfy all eligibility criteria (see section 5.1).

- Variables of Interest: 3-HPMA, 2CyEMA, MHBMA, total NNAL (all expressed as concentration adjusted for creatinine in 24-hour urine), and COHb (expressed as % of saturation of hemoglobin).

- Intercurrent Events (ICEs): All ICEs will be treated as 'treatment policy strategy'. This means that the values of the variable of interest is used regardless of whether the ICEs occur.

- Population-Level Summary Statistic: Geometric mean ratios between each THS arm (THS Blade device, THS Induction Mono device or THS Induction Mid device) and CIG of the BoExp under consideration at Day 5.

12.5.2.1 Baseline Comparability

Demographics and baseline characteristics (as described in section 12.4) will be reported by randomization study arm for the FAS.

Given that the study is randomized, demographics and baseline characteristics are expected to be balanced between study arms. Nevertheless, sex and baseline value of the BoExp will be used as covariates in the statistical model (see section 12.5.2.4).

12.5.2.2 Descriptive Analysis

Descriptive statistics as mentioned in section 12.1.3 for the variables of interest and associated changes from baseline will be reported by randomization study arm for the FAS and by study day. Descriptive statistics stratified by the factor described in section 12.1.1 will also be computed.

12.5.2.3 Missing Data Strategy

In this analysis, some missing data might occur because of missing samples, laboratory measurements errors, etc. The main analysis model (see section 12.5.2.4) assumes that subjects with missing data would have outcome data like those in similar subjects in the same group (MAR assumption). This assumption is aligned with the definition of the secondary estimand.

12.5.2.4 Main Analysis

This analysis will be conducted using the same model as the one described in section 12.5.1.4, except that it will use the FAS instead of the PP and all available data will be included in the model.

In section 12.5.1.5 the criterion to declare the study successful was provided. For the secondary estimand, the same difference will be computed and interpreted exploratorily using the same type I error level as for the primary confirmatory hypothesis.

12.5.2.5 Supplementary Analysis

The model described in section 12.5.1.4 allows contrasting all randomization study arms at Days 1, 2, 3, 4, and 5. The following pairwise comparisons at Days 1, 2, 3, 4, and 5 will be reported, together with their unadjusted p-values and 95%-confidence interval:

- THS arms jointly (THS Blade device, THS Induction Mono device or THS Induction Mid device) vs. CIG
- THS Blade device vs. CIG
- THS Induction Mono device vs. CIG
- THS Induction Mid device vs. CIG

12.6 Secondary Objectives

12.6.1 Key Secondary Objectives

The key secondary objectives are to demonstrate the reduction of additional BoExp to selected HPHC given in Table 4 in smokers who switch from CIGs to THS use compared to those who continue to smoke CIG. The statistical analysis for each of these additional BoExp for each THS arm (THS Blade device, THS Induction Mono device or THS Induction Mid device) will be done similarly to those belonging to the primary objective (except the Success Criteria described in section 12.5.1.5). More specifically, the analyses described as primary estimand (see section 12.5.1.4) can be repeated, replacing the endpoints listed in Table 3 by those of Table 4 and performing the analysis by THS arm sequentially.

The evaluation of the key secondary objectives will be done using a procedure of fixed sequence testing (see Figure 3). This first key secondary objective related to the THS Blade device will only be tested if the primary objective is demonstrated for all THS arms. This fixed sequence of study hypotheses ensures that the overall study-wise risk of type I error is preserved at the 2.5% (see section 12.9.3).

If both the primary and first key secondary objectives are declared successful, then the 2nd key secondary objective will be tested with type I error level of 2.5%, this time using the contrast THS Induction Mono device vs. CIG and the BoExp listed in Table 4. If this 2nd key secondary objective is also declared successful, then the 3rd key secondary objective can be tested similarly, this time with the BoExp listed in Table 4 for the THS Induction Mid device arm. If, along the procedure from the primary objective up to the 3rd key secondary objective, any of the objectives are not declared successful, the sequence testing will stop, and further testing will not be permitted.

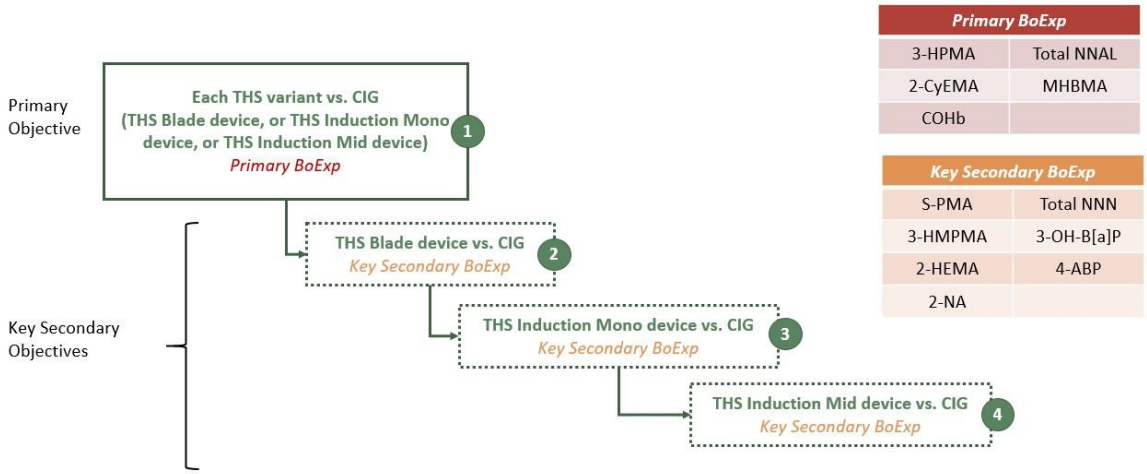


Figure 3 Representation of the Procedure of Fixed Sequence Testing

Note that, at each level of testing, all BoExp need to lead to a statistically significant test. If the statistical test for one of the BoExp for the given arm (or combination of arm) does not reach statistical significance (at the 2.5% level), then the corresponding level of testing cannot be declared successful, and the fixed sequence testing will stop.

The formal testing procedure of this study will use the primary estimand based on the PP (see section 12.3.3). The procedure will be repeated exploratorily using the FAS (see section 12.3.1).

12.7 Other Secondary Objective

All safety analyses will be conducted on the SAF (inferential analyses will not be performed on safety endpoints).

All safety data will be provided in listings by actual exposure arm, subject, and safety period. The safety periods are defined as:

- Screening: from Screening visit to baseline
- Exposure: from Day 1 to Day 5 11:00 PM
- Follow-up: from end of Exposure period to end of Safety follow-up

Unless otherwise specified, summaries will be produced by actual exposure arm and safety periods.

Adverse event data will serve as the primary assessment of safety. Other safety variables monitored in this study will include vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), ECG data, spirometry data, clinical chemistry, hematology, urine analysis safety panel, concomitant medications, body weight, and BMI.

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 by safety period. Summaries will also be presented for AEs leading to product discontinuation, AEs leading to study discontinuation, AEs by relatedness to product exposure (including expectedness) and relatedness to study procedures, AEs by severity, and AE by action taken related to the product. Tabulations will be performed for both the number of subjects experiencing an event and the number of events for the SAF.

With respect to device malfunctions, the number and % of subjects with device events will be tabulated. The number and % of subjects with device events overall, leading to an AE, a SAE, discontinuation, or to non-adherence will also be tabulated.

Descriptive statistics as defined in section 12.1.3 for actual values and changes from baseline will be produced for the following parameters: vital signs, ECGs, spirometry, clinical chemistry, hematology, urinalysis safety panel, body weight, and BMI.

For the other exploratory objectives listed in section 3.3 (exploratory objectives 1, 2 and 4), namely exploratory objectives related to description of NEQ, product use and product experience, descriptive statistics (see section 12.1.3) will be computed for both PP and FAS (see section 12.3).

12.8 Interim Analysis

In this study, no interim analysis is planned.

12.9 Measures to Control Bias

12.9.1 Method for Assigning Subjects to Study Arms

Randomization will be used to assign subjects to study arms. Given that the study is randomized, demographics and baseline characteristics are expected to be balanced between study arms. Nevertheless, sex and baseline value of the BoExp will be used as covariates in the statistical models (see sections 12.5.1.4, 12.5.2.4 and 12.6.1).

12.9.2 Blinding

This is an open-label study. Therefore, the subjects and Investigators or designees or staff will be unblinded to the subject's study arm. However, there will be a limited degree of blinding in the data review and data analysis process. PMP and contract research organization (CRO) personnel will be blinded to the self-selected groups as summarized in Table 12.

Table 12 Blinding Scheme

Blinded Study Personnel	Blinded Data[1]	End of Blinding Period
PMP and CRO study statisticians	Blinded to all BoExp data	After the SAP finalization.
PMP clinical scientists	Blinded to all BoExp data	After the SAP finalization

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

Any PMP and CRO personnel who are not listed in the above table will not be blinded to the study data.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period. PMP 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 independently of the subject identifier to ensure that data cannot be associated to a subject. Unblinded data will only be reviewed by the unblinded study team.

12.9.3 Study Significance Level

In this study, the overall familywise type I error will be preserved at the α-level of 2.5% (1-sided tests will be conducted for the primary and key secondary study hypotheses). This will be done by using a fixed sequence of testing:

- primary objective, then if significant
- 1st key secondary objective, then if significant
- 2nd key secondary objective, then if significant
- 3rd key secondary objective

All objectives will be tested at the 2.5% type I error level until one of the objectives is rejected and no further testing will be performed (in this case, only subsequent exploratory testing will be conducted).

The primary study hypothesis (as assessed using the primary estimand defined in section 12.5.1) will be tested one-sided with a type I error α-level of 2.5%. The associated 1-sided 97.5% confidence interval will be provided. This will be applied to all BoExp of Table 3 that are part of the primary study hypothesis (every BoExp for each THS arms need to pass for the objective to be considered demonstrated).

If the primary study hypothesis is demonstrated, the same α-level of 2.5% will be used for the 1st key secondary hypothesis and the associated 1-sided 97.5% confidence interval will be provided. This will be applied to all BoExp of Table 4 that are part of the 1st key secondary study hypothesis (all need to pass for the THS Blade device arm versus CIG for the 1st key secondary objective to be successful).

If the primary study hypothesis is not demonstrated, the 1st key secondary hypothesis (and all subsequent key secondary objectives) will be considered exploratory and conducted 2-sided at the α-level of 5% and the associated 2-sided 95% confidence interval will be provided.

The analysis will proceed in a similar way for the following key secondary objectives.

For all the exploratory objectives, the statistical tests will be considered exploratory, 2-sided, and conducted at the α-level of 5%. Associated 2-sided 95% confidence intervals will be provided.

12.9.4 Determination of Sample Size and Power Consideration

In this study, 80 healthy smokers will be randomized in a 1:1:1:1 randomization ratio stratified by sex with an overeall quota of 40% per sex to:

- THS Blade device arm
- THS Induction Mono device arm
- THS Induction Mid device arm
- CIG arm

Based on four previous similar studies conducted by PMP on the tobacco heating system (ClinicalTrials.gov identifiers are NCT01970995, NCT01989156, NCT01959932, and NCT01970982, respectively), Table 13 contains estimates of geometric mean ratios (GMR) and associated coefficients of variations (GCV) for the (adjusted) contrast of a tobacco heating system against CIG. The effect of THS is expected to be similar on the selected BoExp. In addition, based on these studies, a conservative estimation of 15% of missing values may be expected for various reasons (e.g., withdrawals, mis-randomization, etc.).

Using the statistics displayed in Table 13, the sample size planned for this study accounting for 15% of missing values (resulting in 20 subject for each THS arms and 20 subjects in CIG arms, respectively), and a one-sided two-sample t-test (on the log-scale) with 2.5% type I error probability, the estimated power for each BoExp is displayed in Table 13. By multiplying the power for each individual BoExp over the four to be tested in the primary hypothesis (per study), a global estimate of power for each THS arm is obtained. Assuming independence of the THS arms, the overall power of the study is equal or larger than 97% $=99\%^3$ (to account for the 3 THS arms) for the primary objective

Note that 10'000 simulations of one-sided two-sample t-test were also conducted to determine the 90 percentiles of the (upper) half-width of the 97.5%-confidence interval (CI) of the ratio between THS arms and CIG, as well as the 90 percentiles of the upper bounds of these CIs. These are also displayed in Table 13. These provide indications on the expected precision on the estimates of the ratios. Table 13 shows that the power of this study for the primary objective is expected to be at least 99%.

Table 13 Power Computation for Primary Objective

NCT (Region)	Endpoint	GMR (%)	GCV (%)	Individual Power	Study-wise Power	90%ile of the upper half width of the 95%-CI	90%ile of the upper bound of the 95%-CI
1970995 (JP)	3-HPMA	50.67	32.72	>99%	>99%	16.0	69.6
	2-CyEMA	18.23	32.43	>99%		6.2	27.8
	COHb	44.94	17.24	>99%		7.2	55.6
	MHBMA	13.49	58.68	>99%		10.1	28.6
	Total NNAL	43.69	26.09	>99%		11.9	60.6
1989156 (US)	3-HPMA	45.77	36.45	>99%	>99%	17.4	68.0
	2-CyEMA	17.21	45.68	>99%		9.9	35.0
	COHb	38.14	26.5	>99%		10.3	51.4
	MHBMA	12.58	76.92	>99%		15.9	35.4
	Total NNAL	43.81	40.7	>99%		18.7	69.7
1959932 (EU)	3-HPMA	41.63	26.1	>99%	>99%	11.1	53.4
	2-CyEMA	13.16	34.41	>99%		4.0	18.6
	COHb	23.45	16.84	>99%		3.8	28.5
	MHBMA	8.38	54.57	>99%		5.6	18.2
	Total NNAL	43.54	27.13	>99%		11.8	61.8
1970982 (JP)	3-HPMA	52.86	39.57	>99%	>99%	21.4	79.5
	2-CyEMA	21.21	43.16	>99%		9.5	33.1
	COHb	47.1	16.08	>99%		6.9	56.1
	MHBMA	23.09	64.59	>99%		14.6	43.0
	Total NNAL	49.03	42.51	>99%		22.8	77.1

Of note, the GMR and GCV are assumptions extracted from the corresponding trial. The columns: individual power and study-wise power are computed through standard formulas. The columns: 90%ile of the upper half width of the 95%-CI and 90%ile of the upper bound of the 95%-CI are simulated values with 20 subjects per arms. The 90%ile of the upper half width of the 95%-CI is a simulated estimate of the precision for the corresponding BoExp. The 90%ile of the upper bound of the 95%-CI is a simulated estimate of the upper bound of the 95%-CI for the corresponding BoExp. Due to the independence of the distributions of the estimates, one cannot deduce the 90%ile of the upper bound of the 95%-CI with the GMR and the 90%ile of the upper half width of the 95%-CI.

A similar reasoning and assumptions for the key secondary objectives can be made. Table 14 displays the power estimates for the key secondary hypothesis. As one can see, each THS arm thus each key secondary objective has a power of at least 99%. By multiplying the power for each objective (≈ 99%) across all 6 objectives (1 primary (union of 3 objectives) + 3 key secondary), the power for all objectives altogether is then estimated to be at least 94% (= 0.94 ≈ 0.99^6, assuming independence of the 6 objectives with a 99% power).

Table 14 Power Computation for Key Secondary Objectives

Study	Endpoint	GMR (%)	GCV (%)	Power	Overall Power	90%ile of the upper half width of the 95%-CI	90%ile of the upper bound of the 95%-CI
1970995 (JP)	2-NA	13.66	33.99	>99%	>99%	5.6	21.5
	3-HMPMA	43.06	35.59	>99%		18.5	72.2
	3-OH-B[a]P	27.19	43.93	>99%		12.9	46.4
	4-ABP	20.10	44.68	>99%		8.2	31.1
	HEMA	50.14	34.79	>99%		14.8	63.2
	S-PMA	10.97	46.63	>99%		7.2	22.0
	Total NNN	27.02	61.84	>99%		23.6	59.9
1989156 (US)	2-NA	12.78	51.37	>99%	>99%	7.6	23.7
	3-HMPMA	38.26	53.56	>99%		21.7	67.8
	3-OH-B[a]P	28.94	54.77	>99%		24.2	67.7
	4-ABP	19.47	63.66	>99%		14.4	38.1
	HEMA	38.67	55.45	>99%		24.2	74.5
	S-PMA	12.58	69.68	>99%		9.6	23.5
	Total NNN	14.06	78.93	>99%		12.2	27.6
1959932 (EU)	2-NA	11.54	36.52	>99%	>99%	4.0	16.9
	3-HMPMA	22.54	30.76	>99%		6.5	31.4
	3-OH-B[a]P	27.50	46.17	>99%		14.0	44.1
	4-ABP	14.94	40.4	>99%		6.4	23.5
	HEMA	32.00	45.75	>99%		18.0	60.6
	S-PMA	5.99	37.3	>99%		2.0	8.3
	Total NNN	24.12	95.15	>99%		27.2	55.6
1970982 (JP)	2-NA	17.62	49.52	>99%	>99%	9.0	30.1
	3-HMPMA	37.71	49.07	>99%		21.3	63.3
	3-OH-B[a]P	29.99	52.2	>99%		19.4	51.9
	4-ABP	18.21	48.07	>99%		9.5	31.3
	HEMA	46.50	44.34	>99%		24.7	81.0
	S-PMA	15.68	49.76	>99%		8.2	25.5
	Total NNN	30.06	67.69	>99%		23.6	65.2

Of note, the GMR and GCV are assumptions extracted from the corresponding trial. The columns: individual power and study-wise power are computed through standard formulas. The columns: 90%ile of the upper half width of the 95%-CI and 90%ile of the upper bound of the 95%-CI are simulated values with 20 subjects per arms.

The 90%ile of the upper half width of the 95%-CI is a simulated estimate of the precision for the corresponding BoExp. The 90%ile of the upper bound of the 95%-CI is a simulated estimate of the upper bound of the 95%-CI for the corresponding BoExp. Due to the independence of the distributions of the estimates, one cannot deduce the 90%ile of the upper bound of the 95%-CI with the GMR and the 90%ile of the upper half width of the 95%-CI.

13 Administrative Considerations

13.1 Study Administrative Structure

13.1.1 Sponsor

The list of sponsor personnel will be provided as a separate document.

13.1.2 List of Principal Investigators and Sites

The list of investigator(s) and site(s) will be provided as a separate document.

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 year 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.

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.), the name or other identifiable details must 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, IEC, or regulatory authorities may inspect their medical records to verify the information collected in the study 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 Investigator(s) and all study site staff involved with the study must permit direct access to source data/documents for study related monitoring, audits, IEC 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 documents must be retained by the Investigator for a minimum of:

- At least 25 years after completion or discontinuation of the study.

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 IEC, composition of the IEC.
- 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).
- 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 for 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. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IEC/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

Investigator(s) 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, IEC, 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).

13.8 Insurance

The Sponsor is responsible for AEs and health damage to participants associated with the products that are used during the study, except for AEs and health damage to patients caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Investigator or the clinical study site or the patients. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

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Appendices

Appendix A Schedule of Events

	Screening	Confinement Period								Early termination [h]	Safety follow-up
Visit (Time Window)		**Admission [g]**	**Baseline**	**Exposure period**					**Discharge**		**+ 3 days post Discharge**
Study Day	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**7 to 9**
Informed consent for study participation	●										
Information smoking risks; smoking cessation advice, and THS briefing	●	●							●	●	
Identification of current cigarette brand	●										
Inclusion/exclusion criteria [a]	●	●									
THS demonstration	●										
Demographics	●										
Medical history, concomitant diseases	●										
Concomitant disease status		●	●	●	●	●	●	●	●		
Prior/concomitant medication	●	●	●	●	●	●	●	●	●	●	●[i]
B: HIV, HBV and HCV	●										
U: Cotinine test	●	●									
U: Drug screen [b]	●	●									
U: Pregnancy test	●	●							●	●	
U: Safety Panel urine analysis	●		●						●	●	
B: Safety panel hematology clinical chemistry	●		●						●	●	

	Screening	Confinement Period							Early termination [h]	Safety follow-up
Visit (Time Window)		**Admission [g]**	**Baseline**	**Exposure period**				**Discharge**		**+ 3 days post Discharge**
Study Day	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**7 to 9**
Alcohol breath test	●										
Vital signs [c]	●	●	●	●	●	●	●	●	●	●	
Physical examination	●										
Body height and weight [d]	●	●									
Spirometry	●		●						●	●	
Electrocardiogram	●		●						●	●	
THS product test		●									
Enrolment		●									
Tobacco/nicotine product use history [e]	●	●									
FTND			●								
Randomization			●								
Informing subjects about allocated				●							
Collection of cigarette butts			●	●	●	●	●	●			
Collection of used THS sticks				●	●	●	●	●			
B: BoExp in blood: COHb			●	●	●	●	●	●			
U: 24-h urine for BoExp (see below)			●	●	●	●	●	●			
ABOUT–Product Experience			●	●	●	●	●	●			
AE/SAE recording [f]	●	●	●	●	●	●	●	●	●	●	
THS product events and complaints		●		●	●	●	●	●	●	●	

Abbreviations: ABOUT = Assessment of Behavioral OUtcomes related to Tobacco and Nicotine Products; AE = Adverse event; B = Blood sample required; BMI = Body mass index; BoExp = Biomarker(s) of exposure; COHb = Carboxyhemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = Human immunodeficiency virus; SAE = Serious adverse event; FTND = Fagerström Test for nicotine dependence; U = Urine sample required.

a) On Day -2 (admission), after eligibility criteria are re-checked, eligible subjects will be enrolled and perform a product test using 2 THS devices. After the product test, subjects not willing to use THS will be discontinued.

b) Urine will be screened for the following drugs: amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and methadone.

c) Systolic and diastolic blood pressure, pulse rate, and respiratory rate.

d) Height will be recorded at Screening visit only and will serve as Baseline value.

e) Tobacco/nicotine product use history: average of daily cigarette consumption recorded at Screening visit and Admission Day -2 will serve as Baseline values.

f) Spontaneous reporting of new AEs/SAEs by the subject and active follow-up of ongoing AEs/SAEs by the site. During the Safety follow-up period, only medication taken for the treatment of AEs will be recorded.

g) Provided the 28-day Screening period has not exceeded, alternate subjects have to repeat the Admission visit Day -2of the following group to re-confirm their eligibility for randomization.

h) If a subject is discontinued from the study, listed Early termination procedures are performed unless the subject refuses to perform the assessments or is Lost to follow-up.

i) Only medication used for AE treatment

Schedule and Sampling Start of 24-hour Urine Collections

	Baseline	**Confinement Exposure Period**				
Study Day	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
BoExp and creatinine in 24-h urine	•	•	•	•	•	•
Bio-banking samples [a]	•	•	•	•	•	•

Abbreviations: BoExp = Biomarker(s) of exposure

a) Collected only if subject has signed optional ICF (section **Error! Reference source not found.**).

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Appendix B Participating Laboratories

Safety Laboratory

[redacted]

Bioanalytical Laboratory

[redacted]

Appendix C Clinical Laboratory Safety Panel

Hematology	Clinical Chemistry	Urine Analysis
- Hematocrit - Hemoglobin - Mean corpuscular hemoglobin - Mean corpuscular hemoglobin concentration - Mean corpuscular volume - Platelet count - Red blood cell count - White blood cell (WBC) count - Differential WBC count: • Neutrophils • Basophils • Eosinophils • Lymphocytes • Monocytes	- Albumin - Total protein - Alkaline phosphatase - Alanine aminotransferase - Aspartate aminotransferase - Blood urea nitrogen - Creatinine - Gamma-glutamyl transferase - Fasting glucose* - Lactate dehydrogenase - Potassium - Sodium - Total bilirubin - Direct bilirubin - Total cholesterol - Triglycerides	- pH - Bilirubin - Glucose - Nitrite - Red blood cell traces - Protein - Specific gravity

* Except at Screening visit or Early termination visit when non-fasting glucose can be assessed

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