PHILIP MORRIS PRODUCTS S.A.

Statistical Analysis Plan

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
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:	31 Oct 2022

STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

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

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1 ABBREVIATIONS OF TERMS

2-CyEMA	2-cyanoethyl mercapturic acid
2-NA	2-aminonaphtalene
3-OH-B[a]P	Total 3-hydroxybenzo(a)pyrene
3-HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-HPMA	3-hydroxypropyl mercapturic acid
4-ABP	4-aminobiphenyl
AE	Adverse event
ATC	Anatomical Therapeutic and Chemical
BMI	Body mass index
BoExp	Biomarker of exposure
BoPH	Biomarker of potential harm
CA35	Classic Auburn 3.5% nicotine
CAF	Caffeine
CM35	Classic Menthol 3.5% nicotine
CI	Confidence interval
CIG	Cigarette
COHb	Carboxyhemoglobin
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CV (statistics)	Coefficient of variation
DHPMA	2,3-dihydroxypropylmercapturic acid
ECG	Electrocardiogram
ENDS	Electronic Nicotine Delivery System
EOS	End of study
FAS	Full analysis set
FDA	Federal Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström Tobacco and Nicotine Dependence

FVC	Forced vital capacity
GCV (statistics)	Geometric coefficient of variation
GMR	Geometric mean ratio
H	Hypothesis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency viruses
HPHC	Harmful and potentially harmful constituents
HPT	Human Puffing Topography
ICF	Informed consent form
ICH	International conference of Helsinki
IEC	International ethic committee
ITT	Intention to treat
IxRS	Interactive web and voice response system
LLOQ	Lower limit of quantification
LS	Least squares
LSMEANS	Least squares means
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
NCT	ClinicalTrial.gov identification number
NEQ	Nicotine Equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
P4M3	Combined CA35 and CM35 arms
PMI	Philip Morris International
PMP	Philip Morris Products SA
PPS	Per protocol set
PT	Preferred term
PX	Paraxanthine
QC	Quality control
RRP	Reduced risk product
S-PMA	*S*-phenylmercapturic acid
SAE	Serious adverse event

SAF	Safety set
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TFL	Tables, figures, and listings
THS	Tobacco Heating System
TNP	Tobacco and/or nicotine containing product
ULOQ	Upper limit of quantification
WBC	White blood cell
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) has been developed to supplement the statistical analyses described in the clinical study protocol (final version 3.0) dated 26-10-2022.

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

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

The preparation of this SAP is based on the following documents:

1. Good Clinical Practice (GCP) guidelines E6 (R1)
2. International Council on Harmonization (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials".
3. ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports".
4. ICH E9 (R1) addendum on “Estimands and sensitivity analysis in clinical trials”.
5. Clinical Study Protocol final version 4.0 dated 13 April 2022.

2.1 Revision History

Version	Date of Revision	Revision
1.0	Refer to electronic signature date	Initial Version
2.0	Refer to electronic signature date	Protocol version 3.0

Summary of changes from previous version

Initial version of the SAP was based on version 2.0 of the protocol. Following the amendment to the protocol, this SAP is amendment to align with the protocol version 3.0. The purpose of that amendment is to change the timepoint for collection of the blood sample for carboxy-haemoglobin measurement to the evening instead of the morning.

In addition, a typing error is corrected (removal of CYP1A2).

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

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. 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. 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 to selected HPHC used as Primary Objectives

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	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.*

The main assessment of the primary objective will be done in subjects who are adherent to their randomized arms (who belong to the Per Protocol Set, see section 8.3).

3.2 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 to selected HPHC used as Secondary Objectives

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 and Endpoints

1. To monitor the safety profile during the study.

   Endpoints
   1. Incidents of adverse events (AEs) and serious adverse events (SAEs)
   2. Incidence of Device malfunction and product complaints (e.g., events related to charger, holder, or sticks)

3. Vital sign changes from baseline (systolic and diastolic blood pressure, heart rate and respiratory rate)
4. Laboratory safety panel changes from baseline
5. Concomitant medication (ConMed)
6. Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT and QTcF intervals)
7. 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 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)

2. 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).

3. 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)

   1. Number of CIG/day
   2. Number of sticks/day

4. 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)

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

3.5 Study Hypotheses and Evaluation Criteria

3.5.1 Hypotheses

The primary study hypothesis is that there is a reduction of each and every of the BoExp to the selected HPHC that are examined for the primary objective, in subjects switching to one of the THS products (THS Blade device, THS Induction Mono and THS Induction Mid) compared to subjects continuing CIG at day 5.

Specifically, the primary hypothesis (H_1) is:

- The geometric mean ratio (THS Blade device/CIG) of 3-HPMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of 2-CyEMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of MHBMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of total NNAL at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of COHb at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 3-HPMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 2-CyEMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of MHBMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of total NNAL at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of COHb at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 3-HPMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 2-CyEMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of MHBMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of total NNAL at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of COHb at Day 5 is less than 1

For the key secondary objective, the hypotheses (H_x) are defined sequentially in this order:

H_2:

- The geometric mean ratio (THS Blade device/CIG) of S-PMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of 2-HEMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of 3-HMPMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of total NNN at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of 3-OH-B[a]P at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of 4-ABP at Day 5 is less than 1

and

- The geometric mean ratio (THS Blade device/CIG) of 2-NA at Day 5 is less than 1

H_3:

- The geometric mean ratio (THS Induction Mono/CIG) of S-PMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 2-HEMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 3-HMPMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of total NNN at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 3-OH-B[a]P at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 4-ABP at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mono/CIG) of 2-NA at Day 5 is less than 1

H_4:

- The geometric mean ratio (THS Induction Mid/CIG) of S-PMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 2-HEMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 3-HMPMA at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of total NNN at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 3-OH-B[a]P at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 4-ABP at Day 5 is less than 1

and

- The geometric mean ratio (THS Induction Mid/CIG) of 2-NA at Day 5 is less than 1

3.5.2 Evaluation Criteria

The study will be declared successful if a reduction is demonstrated for each and every endpoint tested to support the set of primary objectives (3-HPMA, 2-CyEMA, MHBMA, total NNAL, and COHb), using a one-sided test-wise type I error level of 2.5%.

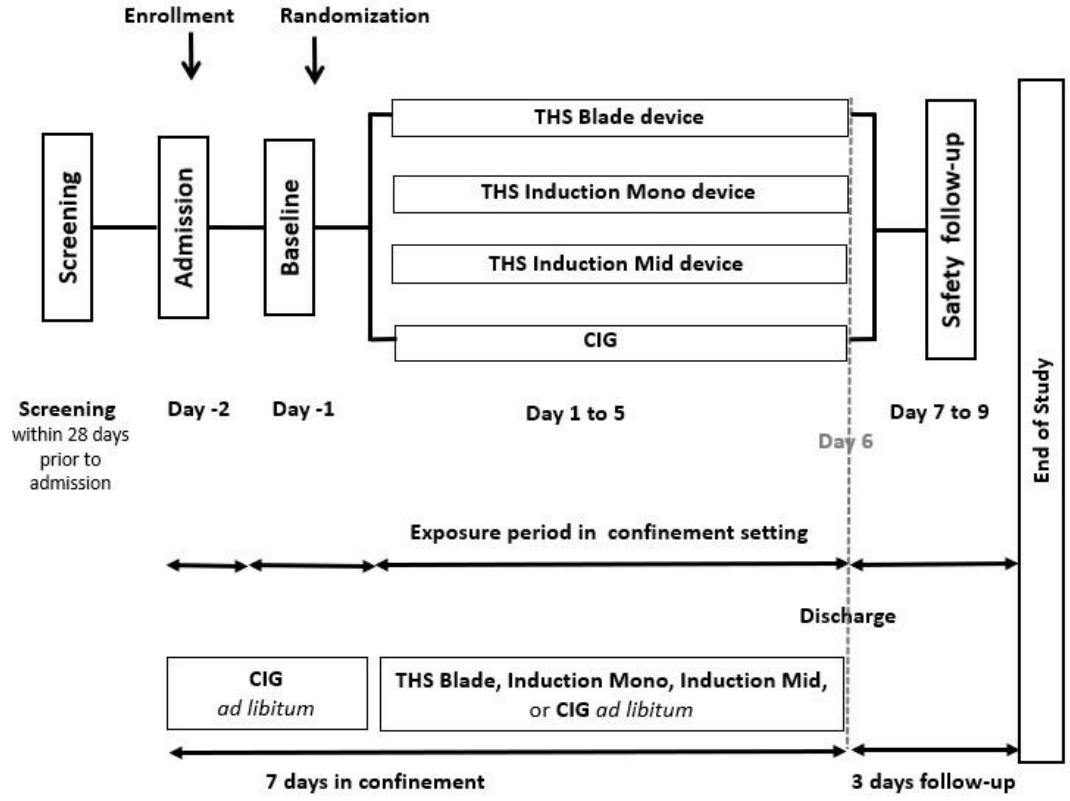
4 INVESTIGATIONAL PLAN

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 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 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 section 13.1). Baseline assessments will be performed as indicated in section 13.1.

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 by sex (details provided in section 4.6.1).

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 to 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. 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" .

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)
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 behaviour.

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), which provide the scientific basis for the development, modification, and validation of PRO measures in support of clinical and regulatory research. The FTND and the ABOUT-Product Experience questionnaires 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.

4.4.1 Timing of Confinement Period

The confinement period will begin after enrolment following admission procedures from Day –2, followed by Baseline assessments and randomization during Day -1. The Exposure period in confinement consists of 5 days (Day 1 to end of Day 5) of *ad libitum* use of the assigned product in each THS and CIG arms.

After Discharge at Day 6 or from the day of early termination, subjects will enter a 3-day Safety follow-up period during which AEs/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs ongoing at Discharge will be conducted by the investigational site.

4.5 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).

4.5.1 Inclusion Criteria

Subjects who meet all inclusion criteria can be enrolled into the study (Table 3)

Table 3. Inclusion Criteria

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

Note: 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.

4.5.2 Exclusion Criteria

Subjects who meet any of the exclusion criteria must not be enrolled into the study (Table 4).

Table 4. Exclusion Criteria

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	

Notes:

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.

4.5.3 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 13.1, 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.

4.5.4 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.

4.5.5 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.

4.6 Product Allocation and Blinding

4.6.1 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.

4.6.2 Blinding

This is an open-label study. Therefore, the subjects and Investigators or designees 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. The protocol deviations will be classified by a blinded team (blinded to the randomization allocation). PMI and contract research organization (CRO) personnel will be blinded to the randomization groups as summarized below in Table 5.

Table 5 Blinding Scheme

Blinded Study Personnel	Blinded Data[1]	End of Blinding Period

PMI and CRO study statisticians	Blinded to all BoExp data	After the SAP finalization (excluding TFL shells finalization)
PMI clinical scientist	Blinded to all BoExp data	After the SAP finalization (excluding TFL shells finalization)

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

4.6.3 Compliance to Product Allocation

During the confinement period, compliance will be ensured by strict distribution and collection of any used and unused THS, comprising of the THS devices and the sticks, and CIG butts by designated investigational site staff. Distribution and return of these products will be documented in appropriate logs.

5 DERIVED AND COMPUTED VARIABLES

5.1 Biomarkers of Exposure

BoExp measured in urine will be expressed as mass concentration adjusted for creatinine in 24-hour urine:

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

where the [ ] indicated concentrations measured from the same 24-h urine collection.

5.1.1 Nicotine Equivalents

The quantity excreted of NEQ over 24 hours will be derived according to the formula below. The concentrations reported for free nicotine and its five major metabolites will not be used as analysis variables.

$$\begin{aligned}\text{NEQ [mg/L]} = (&\text{free nicotine[µmol/L]} + \text{nicotine-glucuronide[µmol/L]} \\ &+ \text{free cotinine[µmol/L]} + \text{cotinine-glucuronide[µmol/L]} \\ &+ \text{free trans-3'-hydroxycotinine[µmol/L]} \\ &+ \text{trans-3'-hydroxycotinine-glucuronide[µmol/L])} \\ &* 162.2[\text{µg/µmol}] \,/\, 1000[\text{µg/mg}]\end{aligned}$$

All concentrations must be in [µmol/L] before applying the above formula. The molecular weights and associated conversion factors from ng/mL to nmol/L are as follows:

Free nicotine	The molecular weight is 162.23 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:54-11-5 [1]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 6.164.
Nicotine-glucuronide	The molecular weight is 338.36 g/mol (National Center for Biotechnology Information (NCBI). PubChem RN:152306-59-7 [2]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.955.
Free cotinine	The molecular weight is 176.21 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:486-56-6 [3]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.675.
Cotinine-glucuronide	The molecular weight is 352.34 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:139427-57-9 [4]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.838.
Free trans-3'-hydroxycotinine	The molecular weight is 192.21 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:34834-67-8 [5]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.203.
Trans-3'-hydroxycotinine-glucuronide	The molecular weight is 368.34 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:132929-88-5 [6]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.715.

The adjustment of NEQ for creatinine in urine will be calculated as described in section 5.1.

5.2 Questionnaires

5.2.1 Tobacco/Nicotine Product Use History

At the Screening visit and at Admission (Day -2), subjects will be asked questions about their TNP use history. The questions will capture frequency and quantity TNP use over the past 4 weeks, and number of continuous years of CIG smoking. This information will be used to assess subjects' eligibility to participate in the study, and to serve as baseline values.

5.2.2 Fagerström Test for Nicotine Dependence (Revised Version)

Level of nicotine dependence will be assessed using a self-reported questionnaire on Baseline Day -1, using the Fagerström Test for Nicotine Dependence (FTND) in its revised version [7].

The questionnaire consists of six questions which will be answered by the subjects themselves. 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) [7]. This information will be used as characteristics of the study subjects.

5.2.3 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 [8].

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) [9] to RRPs and the Product Evaluation Scale [10].

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.

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.

5.3 Categorical Variables

All categorical variables used in this study are listed in Table 6.

Table 6 Categorical Variable Definitions

Variable	Categories	Details
Sex	Female Male	Stratification factor used for randomization and statistical analysis
Race	American Indian OR Alaska Native Asian Black Native Hawaiian OR Other Pacific Islander White	Stratification factor used for statistical analysis
BMI (kg/m^2)	Normal ≥ 18.5 and < 25.0 Overweight ≥ 25.0 and < 30.0 Obese ≥ 30.0 and < 32.0 Note that patients with BMI <18.5 (underweight) and ≥ 32 (Obese) are excluded from the study as per the inclusion/exclusion criteria.	Derived
FTND total score	Mild: 0-3 Moderate: 4-6 Severe: 7-10	Derived

6 SAMPLE SIZE JUSTIFICATION

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

1. THS Blade device arm
2. THS Induction Mono device arm
3. THS Induction Mid device arm
4. 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 7 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 7, 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 7. By multiplying the power for each individual BoExp over the five 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 7. These provide indications on the expected precision on the estimates of the ratios. Table 7 shows that the power of this study for the primary objective is expected to be at least 99%.

Table 7 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 8 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 8 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.

7 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Clarification on exposure period and safety follow-up periods in sections 4.4.1, 9.6.4.4 and 9.6.5.

8 ANALYSIS SETS

8.1 Screened Population

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

8.2 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 (either 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.

8.3 Per Protocol Set (PPS)

The Per Protocol Set (PPS) 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 PPS will be analysed by randomized study arm.

8.4 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.

8.5 Protocol Deviations

Protocol Deviations will be summarized by major with and without impact on evaluability of primary and key secondary objectives and minor categories for the PPS, FAS and SAF. All Protocol Deviation data will be listed.

8.5.1 Major Protocol Deviations

Protocol deviations are defined as any deviation from the procedures defined in the protocol. Major deviations will include, but are not limited to, the categories outlined in Table 9.

Table 9 Major Protocol Deviations with Impact on Evaluability

Category	Description
Any violation of inclusion/exclusion criteria	Considered a major deviation. The blinded data review team will decide on whether it impacts evaluability.
Mis-randomization (wrong information provided to randomization system)	Considered a major deviation with impact on evaluability. Mis-randomized subjects will be classified according to their actual exposure arm for safety analysis.
Use of any nicotine or tobacco-containing product other than the assigned product during the exposure period	Considered a major deviation. The blinded data review team will decide on whether it impacts evaluability.
Assessments related to the primary and key secondary objectives performed outside the time tolerance (see Table 10)	Considered a major deviation. The blinded data review team will decide on whether it impacts evaluability.

8.5.2 Minor Protocol Deviations

Minor deviations may include, but are not limited to, use of concomitant medication and assessments performed outside the time tolerance (see Table 10).

8.5.3 Assessment Time Points and Assessment Time Windows

Table 10 contains the list of assessments that have a time constraint and an acceptable tolerance.

Table 10 Assessment Time Constraints and Time Windows

Related to Primary Objective	Assessment	Time constraint	Tolerance
No	Safety panel Blood sample at Day -1 and Day 6 or during early termination visit	After >= 6 hours of fasting	Not applicable
Yes	BoExp Blood sample at Day -1, 1,2,3,4 and 5	08:00 PM to 10:00 PM	+/- 15 minutes
Yes	24-hours urine	24h	+/- 1 hour

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical evaluation will be performed using SAS®, version 9.4 or higher.

9.1.1 Stratified Presentation

Sex (male and female) is used as a stratification factor during randomization and for the presentation of descriptive statistics. Race will also be used as stratification factor for the presentation of the descriptive statistics.

9.1.2 Sub-group Analyses

No further sub-group analyses are planned.

9.1.3 Descriptive Statistics

All data will be presented in listings, ordered by randomization 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 in addition.

Post-baseline summaries will include change from baseline apart from log-normal variables which will percentage change from baseline.

When applicable, the number and percentage 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 variables frequency counts (n) and percentages (%) will be presented. The number and percentage of subjects with missing data will also be presented.

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

Unless specified otherwise the denominator for percentages will be the total number of subjects (n) in each respective group except missing data.

Continuous safety variables (e.g., clinical laboratory values, vital signs, and ECGs) will be reported to the same precision as the source data. Derived variables will be reported using the same precision as the value(s) from which they were derived. For the reporting of descriptive statistics, the mean and median will be reported to 1 decimal place more than the source data; the minimum, and the maximum values will be presented to the same precision as the source data and standard deviations will be reported to 2 decimal places more than the source data.

9.1.4 Definitions for Statistical Data Analysis

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

9.1.5 Handling of Dropouts or Missing Data

9.1.5.1 Laboratory Parameters

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.

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

1. Questionnaires

Missing data will be handled as follows for the ABOUT – Product Experience Questionnaire.

If there are more than or equal to 50% of within-person item-level missing data within a domain/scale, the missing item-levels will be kept as missing, and the domain/scale score will be set to missing. If there are less than 50% of within-person item-level missing data within a domain/scale, the following rule will be used to produce a complete within-person response pattern:

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

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

3. Calculate a domain/scale score to two significant digits by using all items and the standard formula used when all items are not missing.

For the Fagerström Test for Nicotine Dependence Questionnaire, the total score is set to missing if any of the items is missing. No imputation of missing value will be done for the Nicotine/Tobacco Product Use History Questionnaire.

2. Missing or Partial Dates

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

Table 11. Missing Date information

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

3. Insufficient Data for Analysis/Presentation

If there are no values or events for a planned output, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No adverse events related to study procedures occurred for this study”.

For stratified analyses, strata with <5 subjects overall will not be presented.

9.1.6 Handling of Unplanned Data

If any unplanned assessments do occur, they will be included in listings only. Only planned assessments will be summarized.

9.1.7 Multiple Comparison/Multiplicity

Overall family-wise type I error will be preserved at the 1-sided 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 → 1st key secondary objective → 2nd key secondary objective → 3rd key secondary objective → 4th key secondary objective. All objectives will be tested sequentially in a given order at the 2.5% type I error level until one of the objectives is rejected in which case all subsequent testing will be exploratory 2-sided tests at an α-level of 5%, and the associated 2-sided 95% confidence interval will be reported.

The primary study hypothesis will be tested 1-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 BoExps of Table 1 that are part of the primary study hypothesis. Subsequent analyses of objectives will only proceed if this hypothesis is not rejected.

If the primary study hypothesis is not rejected, 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 reported. This will be applied to all BoExps of Table 2 that are part of the 1st key secondary hypothesis. Subsequent analyses will only proceed if the hypothesis is not rejected.

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

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

9.2 Disposition of Subjects

The number of subjects screened will be provided. The number and percentage (based on the number of subjects screened) of screen failures will also be provided, as well as the reasons

for screen failures. The number and percentage (based on the number of subjects screened) of enrolled but not randomized subjects will also be reported.

Randomized subject disposition will be summarized by absolute counts (n) and percentages (%) and split by randomization arm and overall. Percentages will be based on the number of subjects in each randomization arm or overall. The number of subjects who completed the study, the number of subjects who prematurely discontinued, and the primary reason for withdrawal will be reported.

Disposition data will be listed.

9.3 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized as follows:

- By randomized study arm for the FAS
- By randomized study arm for the PPS
- By randomized study arm or a group of enrolled but not randomized subjects when applicable for the SAF

Demographic variables will include sex, age (years), race, body weight (kg), height (m), body mass index (BMI, kg/m^2). Body weight and BMI will be summarized at screening and admission. Baseline characteristics include TNP use history (average product use per day in the last four weeks, number of participants with continuous product use for the past 3 years, and other questions included in the Nicotine/Tobacco Product Use History questionnaire), spirometry measurements (FEV1, FEV1 % predicted, FVC, FVC % predicted, and FEV1/FVC), and FTND questionnaire score.

All demographic and baseline characteristics data will also be summarized using the stratification factors provided in section 9.1.1.

All demographic and baseline characteristics data will be listed.

9.4 Measurement of Product Compliance

The distribution and return of the THS devices will be documented in appropriate logs. Used THS sticks and CIG butts will be collected and documented for accountability. These data will be presented in listings.

9.5 Extent of Exposure (Product Consumption)

All subjects in one of the THS variant arms (Blade device, or Induction Mono device, or Induction Mid device, respectively) and CIG arms will be permitted *ad libitum* use of the respective products.

This data will be summarised for the FAS, PPS, and SAF, as well as stratified using the factors described in section 9.1.1, as follows:

For the CIG group, the following parameters will be summarized:

1. Number of cigarette butts and percent change from baseline for Day 1, 2, 3, 4, 5,
2. Average number of cigarette butts per day (computed using the sum of all cigarette butts collected over Days 1-5 divided by the number of days spent by the subject in the exposure period) and percent change from baseline,
3. Total cigarette butts over 5 days.

For every THS arms (Blade device, or Induction Mono device, or Induction Mid device, respectively), the following parameters will be summarized:

1. Number of used THS sticks for Day 1, 2, 3, 4, 5,
2. Average number of used THS sticks per day (computed using the sum of all used sticks over Days 1-5 and divided by the number of days spent by the subject in the exposure period),
3. Total number of used sticks over 5 days.

All exposure data will also be listed.

9.6 Planned Statistical Analyses

9.6.1 Primary Objective: Primary Estimand Analysis

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.

9.6.1.1 Primary Estimand

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

1. 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 PPS).

2. Target Population: This is the population of adult smokers who satisfy all eligibility criteria (see section 4.5.1).

3. 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).

4. Intercurrent Events (ICEs):
    1. 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.
    2. 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.
    3. Subjects being tested SARS-CoV-2 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-CoV-2 positive test will be reported as missing.
    4. 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.

5. 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 at Day 5.

9.6.1.2 Main Analysis

The primary analysis will be conducted in the PPS 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=kenwardroger 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 3.1).

For each individual BoExp in the Primary Analysis, the hypothesis 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 1, THS Induction Device 1 or THS Induction Device 2) vs. CIG' of the model described in this section.

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 Primary BoExp.

9.6.1.3 Supportive/Sensitivity Analyses

The model described in section 9.6.1.2 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:

1. THS arms jointly (THS Blade device, THS Induction Mono device or THS Induction Mid device) vs. CIG
2. THS Blade device vs. CIG
3. THS Induction Mono device vs. CIG
4. THS Induction Mid device vs. CIG

Contrasts THS Blade device vs. CIG and THS Induction Mono device vs. CIG and THS Induction Mid device vs. CIG will also be estimated one-sided with a type I error level of 2.5% through the additional 'lsmestimate' statements. These contrasts will be used to assess the key secondary objectives 1, 2 and 3 if the procedure of fixed sequence testing (see section 9.6.3.1) allows.

Descriptive statistics as mentioned in section 9.1.3 for the variables of interest and associated changes from baseline will be reported by randomization study arm for the PPS and by study day. Descriptive statistics stratified by the factor described in section 9.1.1 will also be computed.

9.6.2 Primary Objective: Secondary Estimand Analysis

9.6.2.1 Secondary Estimand

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 PPS. It is defined by the following components:

1. 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).

2. Target Population: This is the population of adult smokers who satisfy all eligibility criteria (see section 4.5.1).

    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).

2. 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.

3. 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.

9.6.2.2 Main Analysis

This analysis will be conducted using the same model as the one described in section 9.6.1.2, except that it will use the FAS instead of the PPS and all available data will be included in the model.

In section 9.6.1.2 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.

9.6.2.3 Supplementary Analysis

The model described in section 9.6.2.3 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:

1. THS arms jointly (THS Blade device, THS Induction Mono device or THS Induction Mid device) vs. CIG
2. THS Blade device vs. CIG
3. THS Induction Mono device vs. CIG
4. THS Induction Mid device vs. CIG

As in the primary estimand analysis, the contrasts THS Blade device vs. CIG and THS Induction Mono device vs. CIG and THS Induction Mid device vs. CIG will also be estimated one-sided with a type I error level of 2.5% through the additional 'lsmestimate' statements provided in section 9.6.1.2 These contrasts will be used exploratorily to assess the key secondary objectives 1, 2 and 3 if the procedure of fixed sequence testing allows.

Descriptive statistics as mentioned in section 9.1.3 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 9.1.1 will also be computed.

9.6.3 Secondary Objective Analyses

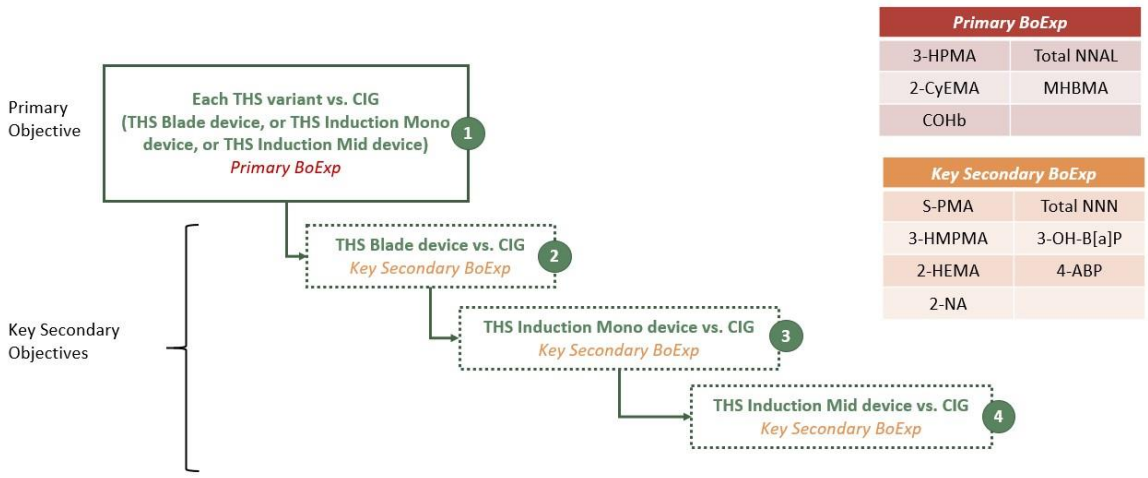
9.6.3.1 Key Secondary Objectives

The key secondary objectives are to demonstrate the reduction of additional BoExp to selected HPHC given in Table 2 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). More specifically, the analyses described as primary estimand (see section 9.6.1.2) can be repeated, replacing the endpoints listed in Table 1 by those of Table 2 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 2). 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%.

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 2. If this 2nd key secondary objective is also declared successful, then the 3rd key secondary objective can be tested similarly 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 2. 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 PPS (see section 8.3). The procedure will be repeated exploratorily using the FAS (see section 8.2).

9.6.3.2 Other Secondary Objective

The secondary objective of this study is to monitor safety and tolerability in all subjects during the study. All safety analyses will be conducted with the SAF (inferential analyses will not be performed on safety endpoints) and are described in 0.

9.6.4 Exploratory Analyses

The exploratory analyses will be conducted using both the FAS and the PPS. Descriptive statistics as described in 9.1.3 will be provided, unstratified, and also using the stratification factors displayed in section 9.1.1. All data (collected and derived) will be listed.

9.6.4.1 Exploratory Objective 1: NEQ

The exploratory objective 1 is related to the analysis of 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. It will be done using descriptive statistics (see section 9.1.3) computed on NEQ (see section 5.1.1 for details of NEQ computations)

9.6.4.2 Exploratory Objective 2: Nicotine/Tobacco Product Use

The exploratory objective 2 related to the nicotine/product use will be covered by the statistics computed as described in section 9.5.

9.6.4.3 Exploratory Objective 3: ABOUT – Product Experience

Data from each item of the ABOUT – Product Experience questionnaire will be summarised as categorical (each possible level per item will be displayed). Subscales will be considered as Safety Evaluation.

9.6.4.4 Adverse Events

AEs (including SAEs) will be collected from the time of ICF signature until the EOS for each participant (AEs occurring on subjects who are not part of the SAF will only be listed and are not part of the summaries related to SAF).

Any AEs which may 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.

Information recorded for AEs/SAEs will include verbatim description, start and stop dates and times, 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).

All safety data will be provided in listings by randomized study arm or a group of enrolled but not randomized subjects, subject, and safety period. The safety periods are defined as:

1. Screening: from Screening visit to baseline
2. Exposure: from Day 1 to Day 5 11:00 PM or early discontinuation date and time
3. Follow-up: from end of exposure to end of Safety follow-up

Unless otherwise specified, summaries will be produced by randomized study arm or a group of enrolled but not randomized subjects and safety periods.

Adverse event data will be used for 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.

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 SAF, overall and by safety period. The number of AEs and SAEs by relatedness to product exposure (including expectedness) and relatedness to study procedures, AEs by severity, and AE by action taken related to the product will be summarized. The number of subjects experiencing an event and the number of events for the SAF will be tabulated. Common adverse events will also be tabulated. Common AEs would be those AEs that have PTs with incidence $\geq$ 5% in any of the randomized study arms or group of enrolled but not randomized subjects.

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

9.6.4.4.1 Serious Adverse Events (Including Deaths)

The number and percentages of SAEs will be summarized overall and by SOC and PT for each randomized study arm or a group of enrolled but not randomized subjects when applicable, for the SAF. Tabulations will include both the number of subjects experiencing an event and the number of events.

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

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

All SAE data will be listed.

9.6.4.4.2 Adverse Events Leading to Discontinuation

Subjects discontinuing the study due to an AE will undergo the early termination procedures and will enter the 3-day Safety Follow-Up Period. If there are any AEs leading to discontinuation of a product or the study, they will be summarized overall and by SOC and PT for the SAF.

All AEs leading to discontinuation will be listed.

9.6.4.5 Device Events

All events relating to the device type will be listed, including event description, device type the event relates to, severity of event, AE relationship, proposed solution and onset/stop dates/times. Device events will be classified according to C54451/Medical_Device_Problem_Codes_FDA_CDRH

A summary table of device events will be presented by randomization arm for both the run-in period and randomized exposure period, including:

- Number of device events and the number and percentage of subjects reporting at least one device event.

- Number of device events and the number and percentage of subjects categorized by severity of device event (minor, major).
- Number of device events and the number and percentage of subjects categorized by AE relationship (related, not related).
- Number of device events and the number and percentage of subjects categorized by event description.

All device events will be listed; data collected during pre-observational period will not be summarized.

9.6.4.6 Medications, Physical Findings, Vital Signs and Other Observations Related to Safety

Clinical Laboratory Evaluation

Table 12 details the clinical laboratory parameters.

Table 12. Clinical Laboratory Parameters Safety Panel

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

Descriptive statistics for actual values and changes from baseline will be produced for the clinical chemistry, hematology, and urinalysis safety panel, for the SAF.

All laboratory data will be listed for all subjects.

9.6.4.6.1 Medical History and Concomitant Disease

Medical history (any condition that started and ended prior to the ICF signature at the Screening visit) and concomitant diseases (any condition detected or ongoing at the time of ICF signature) will be coded using MedDRA and listed separately.

Medical history and concomitant diseases will be summarized by randomized study arm or a group of enrolled but not randomized subjects, SOC and PT for the SAF. The number and percentages of subjects with any medical history/concomitant disease will be presented along with the number and percentage of subjects who record each medical history/concomitant disease by SOC and PT. Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

Medical history and concomitant disease data will be listed for all subjects.

9.6.4.6.2 Prior and Concomitant Medication

All medications will be listed for all enrolled subjects by randomized study arm or a group of enrolled but not randomized subjects when applicable using PT and Anatomical Therapeutic and Chemical (ATC) codes (WHO Drug Global). A flag will be included in the listing to indicate whether the medication is prior or concomitant.

Concomitant medications will be summarized by randomized study arm or a group of enrolled but not randomized subjects for the SAF. The number and percentages of subjects who used the medication at least once will be presented by ATC 1st and 2nd levels and preferred drug name.

9.6.4.6.3 Physical Examination

The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant results will be tabulated for the SAF.

Physical examination data will be listed for all subjects.

9.6.4.6.4 Vital Signs

Actual values and changes from baseline for pulse rate (bpm), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg), respiratory rate (breaths/min), and body temperature (°C) will be summarized as continuous variables (see section 9.1.3) for the SAF.

Vital signs data will be listed for all subjects.

9.6.4.6.5 Spirometry

Actual values and changes from baseline for FEV1, FEV1 % predicted, FVC, FVC % predicted and FEV1/FVC will be summarized as continuous variables (see section 9.1.3) for the SAF.

Spirometry data will be listed for all subjects.

9.6.4.6.6 Electrocardiogram

Actual values and changes from baseline for heart rate (bpm), PR interval (msec), QRS interval (msec), QT interval (msec), and QTcF interval (msec) (corrected according to Fridericia's formula) will be summarized as continuous variables (see section 9.1.3) for the SAF.

Each of ECG parameters mentioned above are classified as being normal, abnormal – clinically significant, abnormal – not clinically significant. The numbers and percentages for these categories, including the combined total abnormal classifications, will be summarized at each visit for the SAF, as described in section 9.1.3. as categorical variables.

ECG data will be listed for all subjects.

9.6.5 Others

Any collected data not included in any of the summaries or listings described above will be listed.

10 ANALYSES AND REPORTING

10.1 Interim Analyses and Data Monitoring

Not applicable.

10.2 Safety Reporting

AEs will be collected from the time the subjects have signed their ICF until the end of the study. The Investigator must notify the sponsor of all SAEs within 24 hours of the first awareness.

Any pregnancy detected after enrolment must be reported by the Investigator to the sponsor within 24 hours of the first awareness and must be followed-up until the pregnancy outcome is reached.

Expedited reporting of SAEs and, if applicable, pregnancies, to competent authorities will be done as locally required.

Information regarding AEs related to THS product events should be actively collected during the study visits. Furthermore, any events of the THS device that do lead to an AE/SAE will follow the same processes as described above.

10.3 Topline Results

Not applicable.

10.4 Final Analyses

Final analyses for this study will be performed after database lock. A data review meeting will be held prior to database lock. This data review meeting will be done on study data by the unblinded team, and the Protocol Deviation classification will be done on blinded data by blinded team.

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

The list of TFLs to be presented will be provided in the separate TFLs shell document.

10.5 ClinicalTrials.Gov Reporting

Statistical summaries to be evaluated for publishing on the clinical trials.gov website will be flagged in the separate TFLs shell document. For some information that will be highlighted in the separate TFLs shell document, the website requires to display statistics for the overall analysis set in addition to the ones per arm. Those statistics will be computed and added to the corresponding tables.

11 DATA PRESENTATION

Unless specified otherwise in this document, data presentation will be consistent with the PMI style guide.

12 REFERENCES

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7. Fagerstrom, K., et al., *The Fagerstrom Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data.* Nicotine and Tobacco Research, 2012. 14(12): p. 1467-73.

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9. Cappelleri, J.C., et al., *Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire.* Addictive Behaviors, 2007. 32: p. 912–923.

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13 APPENDICES

13.1 Schedule of Events

	Screening	Confinement Period								Early termination [i]	Safety follow-up
Visit (Time Window)		**Admission [h]**	**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	●	●	●	●	●	●	●	●	●	●	●[j]
B: HIV, HBV and HCV	●										
U: Cotinine test	●	●									
U: Drug screen [b]	●	●									
U: Pregnancy test	●	●							●	●	
U: Safety Panel urine analysis	●		●						●	●	

	Screening	Confinement Period							Early termination [i]	Safety follow-up
Visit (Time Window)		**Admission [h]**	**Baseline**	**Exposure period**				**Discharge**		**+ 3 days post Discharge**
Study Day	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**7 to 9**
B: Safety panel hematology clinical chemistry	●		●						●	●	
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 [f]			●	●	●	●	●	●			
U: 24-h urine for BoExp (see below)			●	●	●	●	●	●			
ABOUT–Product Experience			●	●	●	●	●	●			
AE/SAE recording [g]	●	●	●	●	●	●	●	●	●	●	
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) The blood sample to measure the BoExp COHb will be collected between 8:00 PM and 9:00 PM.
g) 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.
h) 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.
i) 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.
j) 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 if subject consented to the long-term biobanking

13.2 FTND Scoring Manual

Scoring procedure (FTND_TS2.0 (AU2.0))

Test for Nicotine Dependence (UK-English)			
FTND Question		**Answer**	**Score**
1	How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6 to 30 minutes 31 to 60 minutes After 60 minutes	3 2 1 0
2	Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes No	1 0
3	Which cigarette would you hate most to give up?	The first one in the morning Any other	1 0
4	How many cigarettes per day do you smoke?	10 or less 11 to 20 21 to 30 31 or more	0 1 2 3
5	Do you smoke more frequently during the first hours after awakening than during the rest of the day?	Yes No	1 0

6	Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

The FTND total score is derived by summing the individual item scores if all items are non-missing, otherwise the total score is set to missing. For the FTND total score, descriptive statistics and frequency tables according to the following classification are provided (Fagerström et al. 2012):

Mild 0 – 3

Moderate 4 – 6

Severe 7 – 10

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