PHILIP MORRIS PRODUCTS S.A.

Clinical Study Protocol

Study Number:	P1-PK-12
Study Title:	A single-center, randomized, controlled, open-label study in smoking healthy subjects to investigate the nicotine pharmacokinetic profiles following single use of Tobacco Heating System (THS) with a regular or a menthol stick, compared to smoking of a single combustible cigarette (CIG)
Short title:	Nicotine pharmacokinetics of THS single use of a regular or a menthol stick compared to CIG
Product Name:	Tobacco Heating System (THS) Induction device and regular or menthol sticks
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 3 2000 Neuchâtel, Switzerland
Version:	2.0, Approved
Date:	06 Feb 2023
Authors:	[redacted], PhD, Clinical Scientist [redacted], PhD, Biostatistician [redacted], MD, Medical Safety Officer

Version History

Version	Date	Protocol Update/Amendment
Original Document 1.0	22 Nov 2022	Not applicable
2.0	Refer to electronic signature date	Non-substantial Amendment

SUMMARY OF CHANGES FROM PREVIOUS VERSION

The main purpose of this non-substantial amendment is the correction of typing errors, and the clarification of terms.

For identification of the significant changes, the previous and the amended texts are provided. The new text has been highlighted in bold (e.g. **new text**) and deleted text has been crossed out (e.g. ~~deleted text~~).

Section		Changes
	General	The version number and the revision date were updated accordingly to the most current version and date. The double date for Version 01 was deleted.
Synopsis	**Figure 1**	As there was red underline of the term "period", a clean figure without the red underline.
Synopsis	**Study Design**	Parenthesis added to describe "…prior to admission **(on** Baseline ~~(~~Day -1)…"
Section 4.1	**Figure 2**	As there was red underline of the term "period", a clean figure without the red underline.
Section 8.5	**Reporting and Follow-Up of Pregnancies**	Any pregnancy detected after enrollment must be reported by the Investigator **to Sponsor within 24 hours of first awareness**.
Section 9.2	**Table 4**	Body weight ~~and height~~
Section 10.4	**Risk Management**	In addition, at the end of study, the Sponsor will describe **in the CSR** the quality management approach implemented in the study.
Section 12.7.1	**Blinding**	A certain level of blinding, for study statisticians and study scientists (CRO **personnel**~~alls~~ which will be author of the body SAP)…

Synopsis

Sponsor:

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

Name of Product:

Tobacco Heating System (THS) Induction device and regular or menthol sticks

Study Title:

A single-center, randomized, controlled, open-label study in smoking healthy subjects to investigate the nicotine pharmacokinetic profiles following single use of Tobacco Heating System (THS) with a regular or a menthol stick, compared to smoking of a single combustible cigarette (CIG)

Study Number:

P1-PK-12

Short Title:

Nicotine pharmacokinetics following single use of THS with a regular or a menthol stick compared to CIG

Main Objective and Endpoints:

1. To describe the plasma concentration-time profile of nicotine and derived pharmacokinetic (PK) parameters of a single use of THS with either a regular or a menthol stick or of a single CIG.

Endpoints (Day 1 to Day 3)

Plasma nicotine concentration-time PK parameters (THS regular stick, THS menthol stick, and CIG separately):

- Maximum nicotine plasma concentration [C_{max}]
- Time to the maximum nicotine plasma concentration [T_{max}]
- Area under the curve of nicotine plasma concentration-time computed from T0 to T=24 hours [AUC_{0-24h}]
- Area under the curve of nicotine plasma concentration-time computed from T0 to the subject-specific time of maximum nicotine concentration [$AUC_{0-t'}$]

Secondary Objectives and Endpoints:

1. To evaluate pharmacodynamic (PD) effects (subjective effects) of a single use of a THS with either a regular or a menthol stick or of a single CIG. Endpoints are by investigational product (IP).

Endpoints (Day 1 to Day 3)

- Score of CIG craving by the visual analogue scale (VAS) *Craving* assessment
- Score of IP liking by the VAS *Liking* assessment
- Score of intention to use the IP again by the VAS *Intention to Use Again* assessment

2. To evaluate the safety of test products during the study.

Endpoints

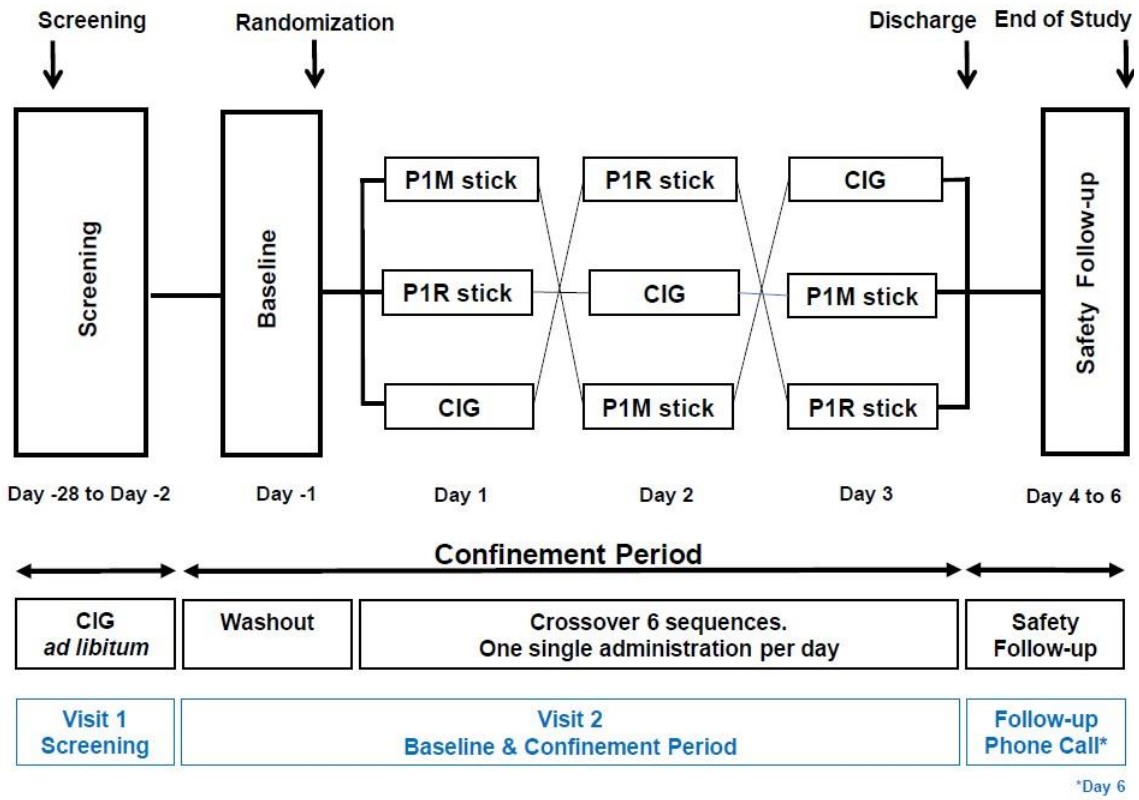
- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of product events
- Changes in electrocardiogram (ECG) from baseline (heart rate, PR, QRS, QT, QTcF interval)
- Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Concomitant medication
- Changes in standard spirometry from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel

Study Hypothesis:

There is no pre-specified hypothesis to be tested in this study. This study aims to obtain PK profiles of the tested products.

Study Design:

This is a single-center, randomized, controlled, open-label, cross-over study in healthy subjects. The study will be conducted with 3 periods and 6 sequences in a cross-over design.



Abbreviations: CIG = combustible cigarette; P1M = menthol taste; P1R = regular taste

Figure 1 Study Design

A Screening visit will be conducted within 27 days (Day -28 to Day -2) prior to admission (on Baseline Day -1) to the investigational site (Figure 1) to check and document the eligibility of the subjects. Investigational site staff will demonstrate the THS (without product use) during the Screening visit. The brand of subjects' cigarettes will be recorded.

Qualified subjects will return to the investigational site for Baseline on Day -1. Subjects will have fasted for at least 6 hours prior to the safety laboratory assessments. After confirmation of eligibility, subjects can be randomized. All subjects who will not be randomized will be documented as screen failures.

Thirty subjects will be randomized to one of 6 possible full crossover sequences of investigational product (IP) use (THS with either regular or menthol stick, and CIG) on Day 1 to Day 3 (see Figure 1). After admission on Baseline Day -1 in the morning, nicotine wash-out will start, and the use of any other tobacco and/or nicotine containing products (TNP) different from the IP assigned for use on Day 1 to Day 3, will not be

allowed. Use of TNP will not be restricted after the subject has been discharged from the investigational site on Day 3.

On Day 1 to Day 3, after at least 23 hours of abstinence from any TNP on Day 1, and after at least 24 hrs of former IP use on Day2 and Day 3 (nicotine wash-out), subjects will smoke a single CIG or perform a single use of a THS either with a regular or a menthol stick, according to randomized product use sequence.

The start of IP use will be defined as T0. T0 on Day 1 to Day 3 should be at approximately the same time in the morning. Venous blood samples will be obtained according to the standard operating procedures (SOPs) at the investigational site. Subjects will report their cigarette craving, IP liking, and intention to use again by performing VAS assessments.

After Discharge on Day 3 or after Early termination following product exposure, the subjects will enter a 3-day Safety follow-up period (SFU period) during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted, concluded per a telephone contact by the investigational site on the last day of the SFU period.

Blood sample collection

On Day 1, fourteen blood samples will be collected for determination of nicotine concentration at the following time points in relation to T0 with a time window as indicated in brackets:

Before T0:

- T_B0 5 minutes before IP use (± 2 minutes)

After T0:

- T_B1 after 4 minutes (± 1 minute)
- T_B2 after 6 minutes (± 1 minute)
- T_B3 after 8 minutes (± 1 minute)
- T_B4 after 10 minutes (± 1 minute)
- T_B5 after 12 minutes (± 1 minutes)
- T_B6 after 15 minutes (± 2 minutes)
- T_B7 after 30 minutes (± 5 minutes)
- T_B8 after 1 hour (± 5 minutes)
- T_B9 after 2 hours (± 5 minutes)
- T_B10 after 4 hours (± 5 minutes)
- T_B11 after 10 hours (± 5 minutes)
- T_B12 after 14 hours (± 5 minutes)

- T_B13 after 24 hours (± 10 minutes)

On Day 2, thirteen blood samples will be collected for determination of nicotine PK after allocated product use at the same time points (without timepoint T_B0). The sample T_B13 of Day 1 will also be used to determine the nicotine baseline concentration prior to T0 on Day 2 and similarly, T_B13 of Day 2 for determination of nicotine baseline concentration prior to T0 on Day 3.

On Day 3, eleven blood samples (T_B1 to T_B11) will be collected for determination of nicotine PK after allocated product use. The samples T_B12 and T_B13 will not be collected.

Questionnaire completion

On Day 1 to Day 3, product liking, cigarette craving, and intention to use the product again will be assessed using a VAS (100 mm going from "strong disliking" to "strong liking" for VAS *Liking*; from "no craving" to "strong craving" for VAS *Craving*; and "very unlikely" to "very likely" for VAS *Intention to Use Again*) at the following time points in relation to T0 with a time window as indicated in brackets:

Prior to T0 (for VAS *Craving* assessment)

- T_V0: within 15 minutes prior to T0

After T0 (for VAS *Craving* assessment)

- T_V1 after 4 minutes (± 2 minutes)
- T_V2 after 10 minutes (± 2 minutes)
- T_V3 after 15 minutes (± 2 minutes)
- T_V4 after 30 minutes (± 2 minutes)
- T_V5 after 10 hours (± 5 minutes)

After T0 (for VAS *Liking* and VAS *Intention to Use Again* assessments)

- Tv3 after 15 minutes (± 1 minute)

Study Population and Main Criteria for Inclusion/Exclusion:

An adequate number of healthy adult female and male smokers who meet all the following eligibility criteria will be screened to ensure that 30 subjects will be randomized.

Inclusion Criteria	Screening	Day -1
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	
4. Subject has continuously smoked on average ≥10 commercially available regular CIG/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	X
6. Subject does not plan to quit smoking within the next three months.	X	X

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

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

Exclusion Criteria	Screening	Day -1
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	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	X
11. The subject has a positive urine drug test.	X	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 Baseline) 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	

Abbreviations:

BMI = body mass index; COVID-19 = Corona virus infection disease; COPD = chronic obstructive pulmonary disease

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

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

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

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

Sample Size:

The sample size is empirically based as there are no considerations for statistical hypotheses. A total of 30 subjects is expected to be sufficient to obtain a precision of 0.2 or lower on the THS / CIG C_{max} ratios.

Investigational Product:

Test product: The THS induction device, and regular and menthol sticks, will be provided by the Sponsor. The following two stick variants will be investigated:

Name in the study	Flavor
P1R stick	Regular
P1M stick	Menthol

Comparator product: The subjects will bring their own supply of commercially available single brand CIG for the study duration.

Duration of Study:

The entire study per subject will last up to 34 days. This will include a screening period of up to 27 days prior to Baseline (Day -28 to Day -2), 4 days of confinement (from the subjects' admission on Day -1 to time of Discharge on Day 3, including 3 overnight stays), and a 3-day Safety follow-up (SFU) period (from time of Discharge on Day 3 or Early termination plus three days). The end of the study (EOS) for a subject is defined as the end of the SFU period. The end of the whole study corresponds to the individual EOS of the last subject.

Statistical Methods:

Demographics and baseline characteristics will be analyzed on the randomized and PK populations.

PK and PD endpoints will be analyzed on the randomized and the PK population.

Safety will be analyzed using the safety population.

Nicotine PK endpoints will be derived from the plasma nicotine concentrations. Nicotine PK parameters will be derived from plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique.

All data will be presented in listings, ordered by subject, study visit, IP and time point, unless otherwise specified.

All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percentage of subjects with missing data, arithmetic means, and standard deviations (mean and SD), median, first and third quartiles, minimum and maximum.

For log normally distributed endpoints ($AUC_{0\text{-}24h}$, C_{max}, and $AUC_{0\text{-}t'}$), geometric mean, geometric CV and geometric CI will be presented in addition.

Categorical variables will be summarized by frequency statistics (number and percentage).

For endpoints relating to sampling times (e.g., T_{max}), only median, first and third quartiles, and minimum and maximum will be presented.

All analyses and summaries will be performed by product.

A mixed-model analysis of variance (ANOVA) will be conducted on $C_{max,}$ $AUC_{0-t'}$, and AUC_{0-24h} endpoints in the natural logarithmic scale. The results of this analysis will be presented in terms of geometric least square mean ratios and 95% confidence intervals (95% CI) for the THS / CIG ratio for both variants of sticks.

The analysis of T_{max} will be conducted using non-parametric tests and Hodges-Lehmann estimates of median difference with its derived 95% CI.

Table of Contents

List of In-Text Tables

List of In-Text Figures

List of Appendices

Abbreviations and Definitions of Terms

Abbreviations

AE	Adverse event
ANOVA	Analysis of variants
AUC	Area under the curve
BLQ	Below limit of quantification
BMI	Body mass index
CIG	Combustible cigarette(s)
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTMS	Clinical trial management system
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
GeoM	Geometric means
GSD	Geometric standard deviation
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IP	Investigational product

IxRS	Interactive web/voice response system
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MRTP	Modified risk tobacco product
PMP	Philip Morris Products S.A.
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SEM	Standard error of the mean
SFU	Safety follow-up
SOP	Standard operating procedure
SRO	Subject reported outcome(s)
T0	Timepoint of start of investigational product use
T_BX	Timepoint of blood collection
THS	Tobacco heating system
TNP	Tobacco and/or nicotine containing product
T_VX	Timepoint of VAS completion
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization

Explanation of Terms

The following special terms are used in this protocol:

Alternate subjects	Subjects who have signed the ICF, have met the eligibility criteria at Screening visit and Baseline Day -1, and have not been randomized due to an adequate number of subjects available for randomization at that time. An alternate subject may join the following group if their 28-day Screening period has not exceeded. The alternate subject will have to repeat the Baseline Day -1 to re-confirm eligibility.
Cigarette(s) (CIG)	The term 'cigarette' refers to commercially available combustible cigarettes (manufactured and hand-rolled) and excludes cigars, pipes, bidis, and other nicotine-containing products.
Early termination (ET)	Premature termination of exposure to the IP after the start of the Exposure period in the confinement setting
End of study (EOS)	The EOS for a subject is defined as Discharge on Day 3 or the date of Early termination of the subject plus the 3 days for the SFU period. The EOS of the entire study is the end of the SFU period for the last subject.
Investigational product (IP)	The IP of this study comprises both the test product, the Tobacco Heating System (THS), and the comparator product, the combustible cigarette (CIG).
Randomization	Allocation of a subject to a particular sequence of IP use.
Screening failure	All subjects who underwent at least one screening procedure and are not randomized (except alternate subjects) will be considered as screen failures. Re-screening of subjects who did not meet any entry criteria will not be permitted.
Stick	Induction tobacco stick, either regular or menthol variant, designed to be used with the THS induction device.
Tobacco Heating System (THS)	Tobacco Heating System (THS) device with Induction technology (device with Induction stick Holder for Induction stick use and separate Charger).

1. Ethics and Regulations

1.1 Independent Ethics Committee (IEC) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] including the subject information sheet, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's brochure [IB], available safety information, curriculum vitae of the Principal Investigator(s) (PI(s)) and designee(s) and/or other evidence of qualifications and any other documents requested by an Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC according to the appropriate provisions found in 21 Code of Federal Regulations (CFR) part 50 ("Informed Consent of Human Subjects") and 21 CFR part 56 ("Institutional Review Boards"). The IEC shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Good Clinical Practice (GCP) [1] and local requirements, as applicable.

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

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

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

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

Relevant safety information will be submitted to the IEC during the study in accordance with national regulations and requirements. Medically qualified study personnel will be available during the study.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [2] and are consistent with ICH/GCP [1] applicable regulatory principles.

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

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

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

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

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

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

1.3.2 Amendment to the Informed Consent Form

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

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, PI(s) or designee(s) abide by the principles of the ICH guidelines on GCP [1]. These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting clinical studies of tobacco products following the United States Food and Drug Administration (FDA) guidelines on modified risk tobacco product (MRTP) [3]. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [2].

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

2 Introduction

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette (CIG) smoking causes pulmonary, cardiovascular and other serious diseases in smokers [4]. The best option for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks that are attributable to smoking, some smokers decide to continue smoking. The development of novel tobacco and/or nicotine containing products (TNP) with the potential to be less harmful as potential alternatives to CIG smoking represents an approach to reduce cigarette-related deaths and diseases among smokers [5].

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

2.1.2 Description of the Product and Scientific Findings

PMP has developed a Tobacco Heating System (THS) with Induction heating technology (marketed under the name of ILUMA™). The THS device consists of a charging unit and a separate stick holder used to heat a tobacco stick. Several taste variants of tobacco sticks are available, e.g., regular, menthol. The temperature of the stick heating is controlled during the use to avoid burning (= combustion) of the tobacco. Further details are provided in the Investigator's Brochure [6].

2.2 Purpose of the Study

The purpose of this study is to describe the nicotine pharmacokinetic (PK) profile during and after single use of THS (Induction heating technology, with either a regular or menthol stick) compared to singular CIG smoking in healthy adult subjects. In addition, pharmacodynamic effects (subjective effects) will be evaluated to provide further insights on product acceptance and likelihood to use the THS again. Safety will be assessed throughout the study.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Information on health risks associated with smoking and smoking cessation advice will be provided at the Screening visit, the Baseline visit on Day -1, and at Discharge on Day 3. The advice will follow the recommendations of the World Health Organization (WHO) "Evidence based Recommendations on the Treatment of Tobacco Dependence" [7]. Subjects who are motivated to quit smoking during the study will be encouraged to do so and will be referred to appropriate medical services for necessary support and counselling. Subjects who participate in this study will also benefit from repeated and detailed health check-ups.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

The potential risk of scheduled procedures in the present study (e.g., blood samples) are deemed to be on par with procedures routinely performed during normal or extended health examinations by the subject's healthcare professional. The total volume of blood to be drawn is approximately 275 mL and does not exceed the levels for a standard blood donation. The risks related to blood sampling include, for example: excessive bleeding, fainting, hematoma, paresthesia, or infection, and those related to the total amount of blood taken over a time span such as weakness, dizziness, or anemia.

2.3.3 Anticipated Foreseeable Risks due to Investigational Products

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

- Transient nicotine withdrawal symptoms (e.g., urge to smoke, irritability, anxiety, restlessness, and difficulty to concentrate) similar to cravings observed during smoking cessation
- Transient symptoms suggesting mild nicotine overdose such as stimulatory effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, and decreased ability to concentrate), gastric acid secretion, and vomiting. Individuals who experience adverse events (AEs) (suggesting excessive stimulant effects) should be instructed to reduce their intensity of product use by decreasing the number of puffs and/or the intensity of puffing
- Change in smoking habits due to study requirements and related concomitant symptoms, e.g., craving.

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

2.3.4 Unforeseeable Risks

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

3 Study Objectives

3.1 Primary Objective(s)

The main objective of this study is:

1. To describe the plasma concentration-time profile of nicotine and derived pharmacokinetic (PK) parameters of the single use of THS with either a regular or a menthol stick or of a single CIG.

Endpoints (Day 1 to Day 3)

Plasma nicotine concentration-time PK parameters (THS regular stick, THS menthol stick, and CIG separately):

- Maximum nicotine plasma concentration [C_{max}]
- Time to the maximum nicotine plasma concentration [T_{max}]
- Area under the curve of nicotine plasma concentration-time computed from T0 to T=24 hours [AUC_{0-24h}]
- Area under the curve of nicotine plasma concentration-time computed from T0 to the subject-specific time of maximum nicotine concentration [$AUC_{0-t'}$]

3.2 Secondary objective

1. To evaluate pharmacodynamic (PD) effects (subjective effects) of a single use of a THS with either a regular or a menthol stick or of a single CIG. Endpoints are by investigational product (IP).

Endpoints (Day 1 to Day 3)

- Score of CIG craving by the visual analogue scale (VAS) *Craving* assessment
- Score of IP liking by the VAS *Liking* assessment
- Score of intention to use the IP again by the VAS *Intention to Use Again* assessment

2. To evaluate the safety of test products during the study.

Endpoints

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of product events
- Changes in electrocardiogram (ECG) from baseline (heart rate, PR, QRS, QT, QTcF interval)

- Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Concomitant medication
- Changes in standard spirometry from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel

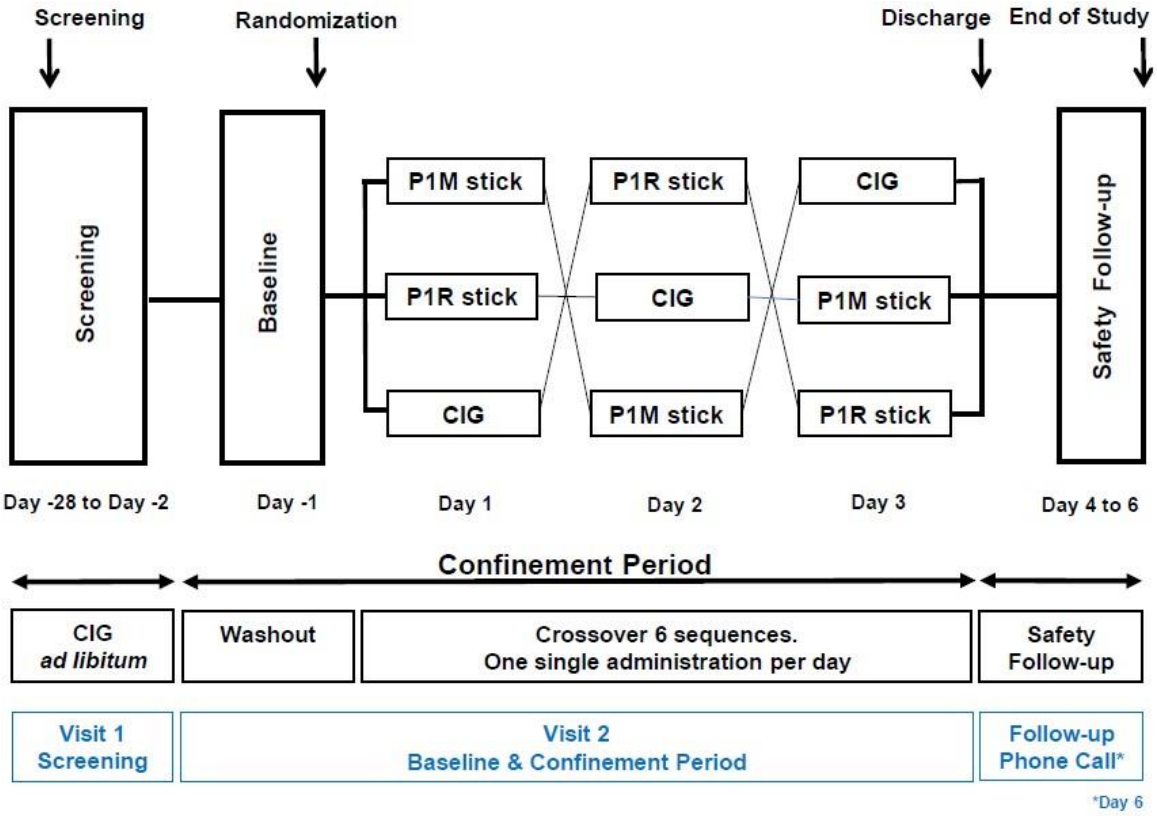
3.3 Success Criteria

Not applicable.

4 Investigational Plan

4.1 Overall Study Design and Plan

This is a single-center, randomized, controlled, open-label, cross-over study in healthy subjects. The study will be conducted with 3 periods and 6 sequences in a full cross-over design.



Abbreviations: CIG = combustible cigarette; P1M = menthol taste; P1R = regular taste

Figure 2 Study Design

A Screening visit will be conducted within 27 days (Day -28 to Day -2) prior to Baseline (Day -1) to check and document the eligibility of the subjects. A demonstration of the THS (without product use) will be done by the investigational site staff during the Screening visit. The brand of subjects' cigarettes will be recorded.

Qualified subjects will return to the investigational site for Baseline on Day -1. Subjects will have fasted for at least 6 hours prior to the safety laboratory assessments and will start abstinence of TNP. After confirmation of eligibility, subjects can be randomized. All

subjects who will not be randomized during their individual Screening period will be documented as screen failures.

Provided that the 28-day Screening period is not exceeded, alternate subjects (not yet randomized) will repeat the Baseline visit of the following group to re-confirm their eligibility for randomization.

Thirty subjects will be randomized to one of 6 possible full crossover sequences of product use (THS with either regular or menthol stick, and CIG) on Day 1 to Day 3. After admission at Baseline Day -1, nicotine wash-out will start, and the use of any other TNP (different from IP assigned for use on Day 1 to Day 3) will not be allowed during confinement at the site. Use of TNP will not be restricted after the subject has been discharged from the investigational site on Day 3.

On Day 1 to Day 3, after at least 23 hours of abstinence from any TNP on Day 1, and at least 24 hours after former IP use on Day 2 and on Day 3 (nicotine wash-out), subjects will smoke a CIG or use the THS either with a regular or a menthol stick according to randomized product use sequence.

The start of use of IP will be defined as T0. T0 on Day 1 to Day 3 should be at approximately the same time in the morning. Venous blood samples will be obtained according to the standard operating procedures (SOPs) at the investigational site. Subjects will report their cigarette craving, IP liking, and intention to use the IP again by completing VAS assessments.

After Discharge on Day 3 or after an Early termination following product exposure, the subjects will enter a 3-day Safety follow-up (SFU) period during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted, concluded per a telephone contact by the investigational site on the last day of the SFU period.

Blood sample collection

On Day 1, fourteen blood samples will be collected for determination of nicotine concentration at the following time points in relation to T0 with a time window as indicated in brackets:

Before T0:

- T_B0 5 minutes before IP use (± 2 minutes)

After T0:

- T_B1 after 4 minutes (± 1 minute)
- T_B2 after 6 minutes (± 1 minute)
- T_B3 after 8 minutes (± 1 minute)

- T_B4 after 10 minutes (± 1 minute)
- T_B5 after 12 minutes (± 1 minutes)
- T_B6 after 15 minutes (± 2 minutes)
- T_B7 after 30 minutes (± 5 minutes)
- T_B8 after 1 hour (± 5 minutes)
- T_B9 after 2 hours (± 5 minutes)
- T_B10 after 4 hours (± 5 minutes)
- T_B11 after 10 hours (± 5 minutes)
- T_B12 after 14 hours (± 5 minutes)
- T_B13 after 24 hours (± 10 minutes)

On Day 2, thirteen blood samples will be collected for determination of nicotine PK after allocated product use at the same time points (without timepoint T_B0). The sample T_B13 of Day 1 will also be used to determine the nicotine baseline concentration prior to T0 on Day 2 and similarly, T_B13 of Day 2 for determination of nicotine baseline concentration prior to T0 on Day 3.

On Day 3, eleven blood samples (T_B1 to T_B11) will be collected for determination of nicotine PK after allocated product use. The samples T_B12 and T_B13 will not be collected.

Questionnaire completion

On Day 1 to Day 3, product liking, cigarette craving, and intention to use the product again will be assessed using a VAS (100 mm going from "strong disliking" to "strong liking" for VAS *Liking*; from "no craving" to "strong craving" for VAS *Craving*; and "very unlikely" to "very likely" for VAS *Intention to Use Again*) at the following time points in relation to T0 with a time window as indicated in brackets:

Prior to T0 (for VAS *Craving* assessment)

- T_V0: within 15 minutes prior to T0

After T0 (for VAS *Craving* assessment)

- T_V1 after 4 minutes (± 2 minutes)
- T_V2 after 10 minutes (± 2 minutes)
- T_V3 after 15 minutes (± 2 minutes)
- T_V4 after 30 minutes (± 2 minutes)
- T_V5 after 10 hours (± 5 minutes)

After T0 (for VAS *Liking* and VAS *Intention to Use Again* assessment)

- Tv3 after 15 minutes (± 1 minute)

4.2 Rationale for Study Design

The single use of a THS with either a regular or menthol stick or of a single CIG will allow appropriate comparison between THS usage and CIG smoking, as well as comparison to published data [8-11].

Sampling time points for determination of nicotine concentrations were selected to ensure reliable estimation of PK parameters. Frequent sampling during the first 15 minutes from T_0 will be performed to reliably assess C_{max}, T_{max}, and AUC.

4.3 Appropriateness of Measurements

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

The Fagerström Test for Nicotine Dependence (FTND) [12, 13] and the visual analogue scale (VAS) assessments of craving, liking, and intention to use the IP again [14-16] used in this study are validated and previously published or adapted versions of validated questionnaires.

4.4 Study Duration

The entire study per subject will last up to 34 days. This will include a screening period of up to 27 days prior to Admission (Day -28 to Day -2), 4 days of confinement (from admission on Day -1 to time of Discharge on Day 3 (3 overnight stays), and a 3-day SFU period (from time of Discharge on Day 3 or Early termination plus three days). The end of the study (EOS) for a subject is defined as the end of the SFU period. The end of the whole study corresponds to the individual EOS of the last subject.

5 Study Population

Thirty healthy female or male adult subjects who have smoked on average at least 10 regular CIG per day for the last 4 weeks prior to Baseline Day -1 will be randomized to one of 6 possible full crossover sequences of IP use (THS with either regular or menthol stick, and CIG) on Day 1 to Day 3. Quotas will be applied to ensure that the randomized population contains at least 40% of both sexes (i.e., at least 12 males and 12 females in the study) overall.

The subjects must have been smoking for at least 3 years prior to the Screening visit. There will be no brand restrictions of CIG. Smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/mL).

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria can be randomized:

Inclusion Criteria	Screening	Day -1
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	
4. Subject has continuously smoked on average ≥10 commercially available regular CIG/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	X
6. Subject does not plan to quit smoking within the next three months.	X	X

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

5.1.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must not be randomized:

Exclusion Criteria	Screening	Day -1
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	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	X
11. The subject has a positive urine drug test.	X	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	

Abbreviations:

BMI = body mass index; COVID-19 = Corona virus infection disease; COPD = chronic obstructive pulmonary disease

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

5.2 Discontinuation of Subjects from the Study

Discontinued subjects 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 Principal Investigator (PI).

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

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

- The early termination procedures for safety assessments will be performed as defined in Section 9.7, 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 PI 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 PI
- Subject unwilling to use the product or to comply with abstinence as required
- An alternate subject that has completed the individual 28-day Screening period and has not been randomized
- The Sponsor terminates the study, or the study terminates at the site. If the Sponsor decides to prematurely terminate the study, the subjects will be promptly informed. The PI or designee should report the fact and the reason in writing to the IEC
- The PI terminates the study or suspends the trial (e.g., due to a loss of key staff members, change of circumstances). If the PI terminates or suspends a trial without prior agreement of the sponsor, the PI 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 reasons:

- 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 randomization will be replaced. Subjects that are discontinued after randomization will not be replaced, except if a need will occur to discontinue all subjects of a treatment group.

5.3 Lost to Follow-up

A reasonable attempt will be made to contact all participants needing to complete or resolve post-study activities (e.g., on-going AEs, end of SFU period phone call). If the subject is not accessible, up to three contact attempts will be made via contact information provided by the subject (e.g., telephone number, cell phone number, email address), allowing one day between attempts for response.

The PI 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 (34 days) without making any contact.

5.4 Violation of Selection Criteria

Detected violations of eligibility criteria post enrollment may require subjects to be discontinued from the study based on a case-by-case decision of the PI. Any subsequent decision on the use of the corresponding samples will be made on a case-by-case basis by the PI.

6 Investigational Products

6.1 Description of Investigational Products

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

6.1.1 Test Product: Tobacco Heating System

The investigational test product examined in this study is the THS Induction Mid device with regular and menthol sticks.

The THS devices and the two variants of the sticks (i.e., regular and menthol) will be supplied by the Sponsor.

The THS device provided by the Sponsor comprises the following components: Charger, Holder, and power supply/charging cable.

6.1.2 Comparator Product

The investigational comparator product in this study will be a regular CIG. The subject's preferred brand of commercially available CIG will not be provided by the Sponsor.

All subjects eligible at Screening visit and invited for Baseline visit Day -1 will be asked to purchase their usual brand of CIG and to provide it to the site personnel at their admission on Baseline (Day -1). Every subject will bring an unopened pack of CIG which will be kept in secured storage room at site with access limited to authorized personnel.

6.1.3 Packaging and Labeling

At Baseline visit (Day -1), all study subjects will provide a sealed pack of CIG (sufficient for the confinement period) to the investigational site staff. The CIG pack provided by the subject should not be opened and the cellophane cover should be intact.

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

THS devices and packs of regular and menthol sticks will be labelled with the necessary information including, but not limited to, product code, expiry date, and notification of limiting THS devices and sticks to investigational use only.

6.2 Use of Investigational Product(s)

Subjects will not be forced to smoke CIG or use THS and will be free to stop smoking CIG/ using THS at any time during the study.

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

6.2.1 Screening Visit (Day -28 to Day -2)

The subjects will be informed how to use the THS, and the site personnel will give a demonstration of the THS use.

6.2.2 Baseline Visit (Day -1)

With the start of the Baseline visit Day -1, subjects will be required to stop smoking CIG and remain abstinent of any use of TNP (except the single use of IP on Day 1 to Day 3 of the exposure period) until completion of the discharge procedures on Day 3.

6.2.3 Exposure Period (Day 1 to Day 3)

On Day 1, after at least 23 hours of abstinence from any TNP on Day 1, and after at least 24 hours on Day 2 and Day 3, subjects will start using their allocated IP (Section 9.3).

According to the randomized sequence, for THS use, subjects will be provided with a fully charged THS holder with a regular stick or menthol stick, switched on for use, at T0 (start of use).

For CIG smoking, subjects will be provided one CIG (lightened up) at T0 (start of use).

6.2.4 Discharge (Day 3)

After completion of the Discharge procedures at the end of Day 3, subjects can use any TNP according to usual habits.

6.2.5 Safety Follow-up Period

During the 3-day Safety follow-up period, subjects can use any TNP according to usual habits.

6.2.6 Stopping Rules for Investigational Product

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

For subjects who are discontinued, the reason for discontinuation should be documented in the source documents and in the Case report form (CRF) and subjects will undertake Early termination procedures (Section 9.7), unless they disagree, or certain procedures have already been performed.

6.3 Method for Assigning Subjects to Product Sequences

On Day -1, following the re-confirmation of eligibility and completion of baseline procedures, the subjects will be randomized to one of the six sequences of the 3-period cross-over design (Figure 2) by means of a permuted-block schema. Details about the randomization process will be documented in the randomization plan that should contain information about number of blocks, block sizes, block pre-allocation process, stratification, storage of the randomization list and study personal blinding requirements.

The following quotas will be applied on the total number of randomized subjects:

- At least 40% of each sex will be represented

If an adequate number of subjects is already randomized to the study sequences, any additional subjects (except alternate subjects) will be discontinued from the study prior to randomization and will enter the 3-day Safety follow-up period (Section 9.6).

Block size and other randomization details will be available in the randomization plan. The randomization scheme will be generated by an independent statistician and neither the Sponsor staff, nor Investigator or study subjects will have access to the randomization scheme during study conduct.

6.4 Blinding

This is an open-label study. Therefore, the subjects, the Investigator, the PMP and CRO personnel will be unblinded to the subject's sequence and product use.

6.5 Investigational Product Accountability and Compliance

6.5.1 Dispensing Investigational Product

From Day 1 until Day 3, the THS, comprising of a fully charged device and a stick (according to randomized sequence), or a CIG will be dispensed by the investigational site staff, as per the study design. Each dispensing of IP to the subject will be recorded in a log.

6.5.2 Storage and Accountability

The THS components and cigarettes will be stored in a secured storage place at the investigational site with access limited to the authorized personnel only. The distribution and return of IP will be controlled by qualified and appropriately trained investigational

site staff. Subjects will return the THS, comprising of the THS device and the used stick, immediately after the IP use to the investigational site staff for accountability.

Smoked CIG will be documented, and CIG butts will be collected by investigational site staff for accountability.

6.5.3 Investigational Product Retention

Used and unused THS devices and sticks will be destroyed or returned to the Sponsor upon study completion. Smoked CIG butts will be destroyed upon study completion.

6.5.4 Compliance to Investigational Products

Compliance will be ensured by strict distribution and collection of any used and unused THS comprising of the THS device and stick, and CIG / CIG butts by designated investigational site staff.

6.6 Restrictions

6.6.1 Smoking Restrictions

During the Screening period, subjects will be allowed to use any TNP according to their usual habits except during the procedures of the Screening Visit (Section 9.1). Spirometry assessments at Screening and at Day -1 will be performed at least one hour after stopping smoking (Sections 9.1 and 9.2).

From Baseline visit (Day -1) to Discharge (Day 3) or Early termination, use of any TNP (except IP use as per study design) will not be permitted.

A nicotine washout period of at least 23 hours should be respected before IP use on Day 1, and of at least 24 hours on Day 2 and Day 3.

6.6.2 Dietary Restrictions

A standard diet will be designed for the whole confinement period. For each meal, the caloric and fat content should be controlled to avoid a “high-fat” diet. The FDA guidance on food-effect studies for bioequivalence testing identifies a “high-fat” diet as a diet which contains “approximately 50 percent of total caloric content of the meal [from fat] and is high in calories (approximately 800 to 1000 calories) [17].”

Subjects are not allowed to bring their own food or beverages to the investigational site. Meals will be served as described in Section 9. Additional light snacks, fruit, and raw vegetables can be distributed to the subjects without restrictions at any time during confinement (except during product use periods) if they comply with the standard diet. Consumption of water is allowed as desired. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed. Subjects should refrain from ingesting foods or beverages

containing grapefruit or Seville-type (sour) oranges and marmalade from 7 days prior to Day -1 and throughout the study. The same menu and meal schedule will be administered uniformly for all subjects. Subjects should have fasted (black coffee or tea without sugar is possible) for at least 6 hours prior to safety laboratory assessments at Day -1.

Subjects should refrain from strenuous and/or unaccustomed exercise throughout the entire course of the study.

6.7 Concomitant Medication

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

Medications will be allowed and carefully monitored during the study by the PI or designee. The PI(s) is(are) responsible for the medical care including medication of the subjects during their participation in the study. Any decisions regarding the prescription of medication will be taken in the best interest of the subject. The use of any concomitant medication must be fully documented in the source document and transcribed into the CRF.

7 Study Procedures

Investigational site staff performing or recording study assessments must have the appropriate and fully documented training. An overview of study assessments and time points is shown in the schedule of events (Appendix A). Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care. Site personnel will adhere to the site's standard operating procedures (SOPs) for study-related procedures.

7.1 Informed Consent

Subjects will be asked to provide their written informed consent to participate in the study (Section 1.3). Study assessments must only start after the time of ICF signature by the subject.

7.2 Information on the Risk of Smoking, Smoking Cessation Advice, and THS Briefing

At the Screening visit, on Baseline Day -1 (before randomization) and at Discharge (Day 3), subjects will receive i) information on the risks of smoking, ii) smoking cessation advice, and iii) briefing on THS (e.g., that its use is not risk-free) as described in the Schedule of Events (Appendix A).

The information on the risk of smoking and advice on smoking cessation will take the form of a brief interview according to the WHO recommendations [7]. The briefing of subjects on THS will address any intended or unintended beliefs that subjects may have about THS. The goal of the debriefing is to help ensure that subjects enter and exit the study with an accurate understanding of the product risks.

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

7.3 Support During Abstinence from any Tobacco and Nicotine Containing Products

Subjects will be offered support during periods of abstinence from any TNP during the study from Day -1 to Discharge on Day 3 by the PI and/or investigational site staff. Support resources will include counselling and assistance, entertainment, monitoring of the subject's behavior, AEs, and the subject's mood, clinical tests e.g., vital signs, physical examination.

7.4 Clinical Assessments

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

7.4.1 Demographic Data

Sex, date of birth, and race will be recorded for each subject as described in the Schedule of Events (Appendix A).

7.4.2 Medical History, Concomitant Disease, Previous and Concomitant Medications

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

Prior medication taken within 4 weeks prior to the Screening visit and any concomitant medication will be documented. Any medication started prior to the Screening visit and still being taken by the subject will be considered concomitant medication. Medication initiated after the Screening visit will also be referred to as concomitant medication. The definition of concomitant medication applies to both prescribed and over-the-counter products.

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

7.4.3 Physical Examination

Physical examinations will be conducted as described in the Schedule of Events; the examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, thyroid gland, chest, lungs, back, abdomen, dentition, gastrointestinal,

cardiovascular, musculoskeletal, and neurological systems. The physical examination is to be conducted by the PI or designated fully trained representative.

7.4.4 Body Height and Weight

Body height and weight will be recorded at the Screening Visit and body-mass-index (BMI) will be calculated using the following formula:

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

The BMI will be used to assess eligibility for enrolment.

7.4.5 Vital Signs

The vital signs (systolic and diastolic blood pressure, respiratory rate, and pulse rate) will be measured as described in the Schedule of Events (Appendix A). On Day 1 to Day 3, vital signs will be assessed prior to T0.

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

The PI will define vital sign ranges to determine normal or abnormal results. For those results outside of the normal range, the PI will determine appropriate follow-up including reporting of any AEs.

7.4.6 Spirometry

Spirometry (without bronchodilator) will be performed at the Screening visit, Baseline Day -1 and at Discharge (Day 3) or Early termination in accordance with the 2019 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry [18, 19]. Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set [20].

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

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

The Investigator will define Spirometry ranges to determine normal or abnormal results. For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

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

7.4.7 Electrocardiogram

At the Screening visit, Baseline Day -1 and at Discharge (Day 3) or Early termination, a standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position as described in the Schedule of Events.

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

The Investigator will define ECG ranges to determine normal or abnormal results. For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

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

7.5 Laboratory Assessments

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

Hematology and clinical chemistry analysis will be assessed as per Schedule of Events. Subjects should have fasted for at least 6 hours prior to safety laboratory assessments, except at Discharge and Early termination where non-fasting samples can be used. Tests will be conducted at a local laboratory (Appendix B). If during the Screening visit a blood sample is not suitable for analysis (e.g., blood clotting) a re-test should be performed for the specific parameters which are not available. Safety urine analysis will be assessed at Screening, Baseline and at Discharge or at Early termination.

Parameters to be tested are listed in Table 1.

Table 1 Clinical Laboratory Parameters for Safety Panel

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

*Differential WBC count both percentage and absolute

7.5.2 Serology

Tests for hepatitis B virus (HbsAg), hepatitis C virus (HCV antibody) and human immunodeficiency virus (anti-HIV1/2) will be performed at the Screening visit. In case of positive results, the subject will be referred to appropriate medical care.

7.5.3 Urine Drug Screening

A urine drug screen including testing for alcohol will be performed at the site at the Screening Visit and at Baseline Day -1. The urine will be screened for:

- amphetamine type substances
- barbiturates
- benzodiazepines
- cannabinoids
- cocaine
- opiates
- methadone.

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

7.5.4 Urine Cotinine Screening

A urine cotinine test will be performed to confirm the TNP use status as described in the Schedule of Events.

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

7.5.5 Alcohol BreathTest

An alcohol breath test will be performed in all subjects as described in the Schedule of Events.

7.5.6 Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects as per Schedule of Events. Subjects with a positive urine pregnancy test or unclear results (from two repetitions) before randomization will be considered as screen failures.

In case of any positive pregnancy test, the PI or designee will inform the subject about the risks associated with smoking during pregnancy and subjects will be referred to a health care facility/health care provider for pregnancy follow-up.

All pregnancies detected during the study must be reported and handled as described in Section 8.5. Pregnancies detected after randomization will lead to discontinuation from the study Section 5.2).

7.6 Sample Handling, Storage, and Shipment

7.6.1 Urine samples

Urine drug test including testing for alcohol, urine pregnancy tests and urine cotinine tests will be done by the site personnel at the site. All other blood and urine samples will be managed by the laboratory designated in Appendix B.

Detailed procedures for handling of samples are described in a separate document. Safety laboratory samples will be destroyed as per laboratory local regulations. All other samples will be destroyed post database lock or post finalization of the bioanalytical reports, whichever occurs last. The facility/-ies at which the samples are stored will be informed in writing by the Sponsor when destruction of the samples shall be performed.

7.6.2 Blood Samples

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

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

In total, approximately 275 mL of blood will be collected for this study including samples for determination of plasma nicotine concentrations (approximately 190 mL), serology (5 mL) and safety laboratory (approximately 60 mL, or 80 ml for alternate subjects). This calculation is based on an individual volume of each sample of 5.0 mL for nicotine PK, 5 mL for serology, and 20 mL per safety laboratory assessments. The total volume of blood drawn will not exceed the levels for a standard blood donation.

Details on the procedures for collection, labeling, handling and shipment of samples are described in the laboratory manual.

7.7 Other Study Procedures

7.7.1 Investigational Product Demonstration

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

7.8 Questionnaires

The questionnaires will be completed by the subject as described in Section 9, and the Schedule of Events (Appendix A). Completion at later time points will be considered as a protocol deviation. All subject-reported outcome as well as instructions will be provided in the subject's local language. Details of the assessments are provided in Appendix C and in Appendix D.

7.8.1 Fagerström Test for Nicotine Dependence (Revised Version)

At the Screening visit, potential nicotine dependence will be assessed as per Schedule of Event using the FTND in its revised version as updated in 2012 [21].

The questionnaire consists of six questions which are to be answered by the subjects themselves. The scores obtained on the test will permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) [21].

7.8.2 Tobacco/Nicotine Product Use History

At Screening visit and Baseline visit Day -1, subjects will be asked questions about their TNP use history. The questions will capture frequency and quantity of TNP use over the past four weeks, the flavor of CIG the subjects do smoke, the number of continuous years of CIG smoking, the duration of cessation attempts over the past three years, and the intention to quit smoking within the next 3 months. This information will be used as characteristics of the study subjects, to assess their eligibility to participate in the study, and to serve as baseline values.

7.8.3 VAS Craving Assessment

At the time points specified in Section 4.1, craving for CIG will be evaluated using a one-item self-reported VAS *Craving* assessment [14], asking subjects to rate craving for CIG (*How strong is your craving for cigarettes?),* on a 100 mm unipolar scale, ranging from 0 (no craving) to 100 (strong craving).

7.8.4 VAS Liking Assessment

Product liking for the THS or the CIG used and smoked as part of the study will be evaluated using a one-item self-reported VAS *Liking* assessment, asking subjects to rate liking for the product *(Overall, my liking for this product is:)* on a 100 mm bipolar scale, ranging from 0 (strong disliking) to 100 (strong liking), with a neutral middle point, as recommended in the FDA guidance for industry on abuse liability assessment [15].

7.8.5 VAS Intention to Use Again Assessment

The intention to use the THS or the CIG again will be evaluated using a one-item self-reported VAS *Intention to Use Again* assessment, asking subjects to rate their intention to use the IP again (*How likely are you to use this product again?*) on a 100 mm bipolar scale, ranging from 0 (very unlikely) to 100 (very likely) [16] .

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Events

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

8.1.2 Serious Adverse Events

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

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

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

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

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

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

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

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Information

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

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

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

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

8.2.2 Period of Collection

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

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

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

8.2.3 Intensity of Adverse Event

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

Table 2 Intensity of Adverse Events

Mild:	Easily tolerated, not interfering with normal everyday activities
Moderate:	Interferes with normal everyday activities, but the subject is still able to function

Severe: Incapacitating and requiring medical intervention

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

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

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

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

8.2.5 Expectedness

Any AE assessed as related to the IP (THS or CIG) will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with information already recorded in Section 6.7 of the current Investigator's Brochure [6].

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

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

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

All SAEs will be followed up by the Investigator or designee after the end of the SFU period, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). In case the subject cannot

be reached for additional information related to SAE(s), a total 3 attempts should be performed before the subject will be declared as lost to follow-up.

8.3 Reporting Serious Adverse Events

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

Follow-up information should be reported on a new SAE report form, marked as a follow-up report and submitted to Sponsor according to the same timelines as described above. The follow-up SAE report form must include the minimum information required for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

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

8.4 Reporting of Other Abnormal Findings

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

8.5 Reporting and Follow-Up of Pregnancies

8.5.1 Period of Collection and Follow-up

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

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

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

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

8.5.2 Reporting of Pregnancies

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

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the Early termination (Section 9.6), as soon as practical after discontinuation and will enter the 3-day SFU period.

Any AEs or SAEs that are ongoing at the end of the SFU period will be managed as described in Section 8.2.6.

8.7 Device Malfunction, Product Complaints and Misuse

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

Minor – Can be resolved easily.

Major – Cannot be resolved.

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

Any test product misuse may result in use-related hazards (Section 2.3.3).

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

9 Study Activities

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

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

The main objective for this study is the evaluation of the plasma concentration-time profile of nicotine and derived PK parameters. Therefore, the collection of blood samples for determination of plasma nicotine concentration should be as close to the schedule time as possible and should take precedence over any other assessments required at the same time.

9.1 Screening Visit (Day -28 to Day -2)

The Screening visit will be performed ≤27 days prior to potential randomization at Baseline Day -1. First, the Informed consent form (ICF) along with study information will be given to the subject. Prior to being asked to sign the consent form, subjects will be given time to review the study information and ask any questions. When/if the ICF is signed and dated and timed, the screening procedures (Table 3) can be performed in the order deemed most practical. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed at the Screening visit.

If the inclusion and exclusion criteria are satisfactorily met after Screening visit (including negative pregnancy test for female), the site staff will call the subject to arrange the Baseline visit (Day -1) to the site.

Table 3 Time Schedule – Screening Visit

Time	Procedures	Additional Information
Prior to any other study procedure	Informed consent process and signature of ICF	
During the Visit	Information on smoking risks, advice on smoking cessation	Incl. THS briefing
	Demographics	
	Medical History	Incl. concomitant diseases
	Concomitant medication	Incl. during ≤4 weeks
	Body weight and height	BMI
	FTND questionnaire	Nicotine dependence
	TNP Use History questionnaire	Smoking history

	Physical examination	
	Vital signs	≥5 min supine rest ≥15 min TNP abstinence
	ECG	≥10 min supine rest
	Spirometry	≥15 min sitting rest ≥1 hr TNP abstinence
	Serology	HBV, HCV, and HIV
	Venous blood sample	- Safety panel (hematology and clinical chemistry)
	Spot urine sample	- Safety panel - Drug test - Cotinine test - Pregnancy test (female)
	Alcohol breath test	
	THS demonstration	Without product use
	Identification of current CIG brand	Explain CIG provision for confinement period by subject
	AE/SAE recording	
	Review of eligibility criteria	Incl. subject's willingness to comply with study procedures, particularly periods of TNP abstinence

Abbreviations:

AE = Adverse event; BMI = Body mass index; ECG = electrocardiogram; CIG = combustible cigarette; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hr = hour; ICF = informed consent form; Incl. = including; min = minute; SAE = Serious adverse event; THS = tobacco heating system; TNP = tobacco and/or nicotine containing product.

9.2 Baseline Visit Day -1

At the Baseline visit Day -1, if the subject's eligibility will be confirmed [1] by the procedures shown in Table 4. The subject eligible for randomization must abstain from any TNP, to ensure at least 23 hours of nicotine wash-out ahead of the IP exposure on Day 1.

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

Table 4 Time Schedule – Baseline Visit

Time	Procedures	Additional Information
Start of the Visit	Stop of TNP use	To ensure ≥23 hours of nicotine wash-out
During the Visit	TNP Use History questionnaire	Smoking history
	Information on smoking risks, advice on smoking cessation	Incl. THS briefing
	Concomitant disease / concomitant medication	Since Screening visit
	Body weight	BMI
	Vital signs	≥5 min supine rest ≥15 min TNP abstinence
	ECG	≥10 min supine rest
	Spirometry	≥15 min sitting rest ≥1 hr TNP abstinence
	Venous blood sample	- Safety panel (hematology and clinical chemistry)
	Spot urine sample	- Safety panel - Drug test - Cotinine test - Pregnancy test (female)
	Alcohol breath test	
	Review of eligibility criteria	Incl. subject's willingness to comply with study procedures
	Randomization	
	AE/SAE recording	

Abbreviations:

AE = Adverse event; ECG = electrocardiogram; hr = hour; Incl. = including; min = minute; SAE = Serious adverse event; TNP = tobacco and/or nicotine containing product.

9.3 Day 1

The study procedures performed on Day 1 are listed in Table 5.

Table 5 Time Schedule – Day 1

Time	Procedures	Additional Information
Prior to T0	Vital signs	≥5 min supine rest
Prior to T0	VAS *Craving* T_V0	≤15 min prior to T0

Prior to T0	Blood sample T_B0	≤5 min (±2 min) prior to T0
Just before T0	Switch-on of THS (with stick) or lighting of CIG	Performed by investigational site staff
T0	Start of IP use	
During / after IP use	Blood sampling (nicotine PK)	Post-T0 time points: T_B1 after 4 minutes (± 1 min) T_B2 after 6 min (± 1 min) T_B3 after 8 min (± 1 min) T_B4 after 10 min (± 1 min) T_B5 after 12 min (± 1 min) T_B6 after 15 min (± 2 min) T_B7 after 30 min (± 5 min) T_B8 after 1 hr (± 5 min) T_B9 after 2 hrs (± 5 min) T_B10 after 4 hrs (± 5 min) T_B11 after 10 hrs (± 5 min) T_B12 after 14 hrs (± 5 min) T_B13 after 24 hrs (± 10 min)
	VAS *Craving*	Post-T0 time points T_V1 after 4 min (± 2 min) T_V2 after 10 min (± 2 min) T_V3 after 15 min (± 2 min) T_V4 after 30 min (± 2 min) T_V5 after 10 hrs (± 5 min)
	VAS *Liking* and VAS *Intention to Use Again*	T_V3 after 15 min (± 1 min)
≤2 hours after T0	Breakfast	
≥4 hours after T0	Lunch	
Ongoing	Nicotine wash-out	Optional: snacks and water
	Support during TNP abstinence period	
	Concomitant disease / concomitant medication	
	AE/SAE recording	
	Product events	Malfunction / misuse

Abbreviations:

AE = Adverse event; CIG = combustible cigarette; hr(s) = hours; min = minute(s); IP = investigational product; PK = Pharmacokinetic; SAE = Serious adverse event; T0 = start of IP use; T_BX = time point blood sampling; T_VX = time point VAS assessment; THS = Tobacco Heating System; VAS = Visual analogue scale

9.4 Day 2

The study activities performed on Day 2 are listed in Table 6:

Table 6 Time Schedule – Day 2

Time	Procedures	Additional Information
Prior to T0	Vital signs	≥5 min supine rest
Prior to T0	VAS *Craving* T_V0	≤15 min prior to T0
≤5 min prior to T0	Blood sample T_B14	Day 1 sample T_B13 (24 hrs ±10 min) = T_B0 of Day 2
Just before T0	Switch-on of THS (with stick) or lighting of CIG	Performed by investigational site staff
T0	Start of IP use	
During / after IP use	Blood sampling (nicotine PK)	Post-T0 time points: T_B1 after 4 minutes (± 1 min) T_B2 after 6 min (± 1 min) T_B3 after 8 min (± 1 min) T_B4 after 10 min (± 1 min) T_B5 after 12 min (± 1 min) T_B6 after 15 min (± 2 min) T_B7 after 30 min (± 5 min) T_B8 after 1 hr (± 5 min) T_B9 after 2 hrs (± 5 min) T_B10 after 4 hrs (± 5 min) T_B11 after 10 hrs (± 5 min) T_B12 after 14 hrs (± 5 min) T_B13 after 24 hrs (± 10 min)
	VAS *Craving*	Post-T0 time points T_V1 after 4 min (± 2 min) T_V2 after 10 min (± 2 min) T_V3 after 15 min (± 2 min) T_V4 after 30 min (± 2 min) T_V5 after 10 hrs (± 5 min)
	VAS *Liking* and VAS *Intention to Use Again*	T_V3 after 15 min (± 1 min)
≤2 hours after T0	Breakfast	
≥4 hours after T0	Lunch	

Ongoing	Nicotine wash-out	Optional: snacks and water
	Support during TNP abstinence period	
	Concomitant disease / concomitant medication	
	AE/SAE recording	
	Product events	Malfunction / misuse

Abbreviations:

AE = Adverse event; CIG = combustible cigarette; hr(s) = hours; min = minute(s); IP = investigational product; PK = Pharmacokinetic; SAE = Serious adverse event; T0 = start of IP use; T_BX = time point blood sampling; T_VX = time point VAS assessment; THS = Tobacco Heating System; VAS = Visual analogue scale

9.5 Day 3

The study activities performed on Day 3 before and during IP exposure, and prior to the time of discharge are presented in Table 7.

Table 7 Time Schedule – Day 3

Time	Procedures	Additional Information
Prior to T0	Vital signs	≥5 min supine rest
Prior to T0	VAS *Craving* T_V0	≤15 min prior to T0
≤5 min prior to T0	Blood sample T_B14	Day 2 sample T_B13 (24 hrs ±10 min) ≡ T_B0 of Day 3
Just before T0	Switch-on of THS (with stick) or lighting of CIG	Performed by investigational site staff
T0	Start of IP use	
During / after IP use	Blood sampling (nicotine PK)	Post-T0 time points: T_B1 after 4 minutes (± 1 min) T_B2 after 6 min (± 1 min) T_B3 after 8 min (± 1 min) T_B4 after 10 min (± 1 min) T_B5 after 12 min (± 1 min) T_B6 after 15 min (± 2 min) T_B7 after 30 min (± 5 min) T_B8 after 1 hr (± 5 min) T_B9 after 2 hrs (± 5 min) T_B10 after 4 hrs (± 5 min) T_B11 after 10 hrs (± 5 min)

	VAS *Craving*	Post-T0 time points T_V1 after 4 min (± 2 min) T_V2 after 10 min (± 2 min) T_V3 after 15 min (± 2 min) T_V4 after 30 min (± 2 min) T_V5 after 10 hrs (± 5 min)
	VAS *Liking* and VAS *Intention to Use Again*	T_V3 after 15 min (± 1 min)
Ongoing	Support during TNP abstinence period	
≤2 hours after T0	Breakfast	
	ECG	≥10 min supine rest
	Spirometry	≥15 min sitting rest
	Venous blood sample	- Safety panel hematology and clinical chemistry
	Spot urine sample	- Safety panel - Pregnancy test (female)
≥4 hours after T0	Lunch	
	Vital signs	≥5 min supine rest
	Concomitant disease / concomitant medication	
	AE/SAE recording	
	Product events	Malfunction / misuse
	Information on smoking risks, advice on smoking cessation	Incl. THS briefing
	Discharge	Stop of TNP abstinence

Abbreviations:

AE = Adverse event; CIG = combustible cigarette; ECG = electrocardiogram; hr(s) = hours; IP = investigational product; min = minute(s); PK = Pharmacokinetic; SAE = Serious adverse event; T0 = start of IP use; T_BX = time point blood sampling; T_VX = time point VAS assessment; THS = Tobacco Heating System; TNP = tobacco and/or nicotine containing product; VAS = Visual analogue scale

9.6 Safety Follow-up Period

All subjects participating in the Baseline visit will enter a 3-day Safety follow-up (SFU) period at the time of Discontinuation from the study, even if they are not randomized into the study, unless they are Lost to follow-up.

After Discharge on Day 3, or after Early termination, the subject will enter a 3-day SFU period. During this 3-day period, there will be spontaneous reporting by the subject of new AEs and new SAEs. Any ongoing AEs/SAEs will be actively followed-up by the site. The SFU period is concluded by a phone contact to the subject on the last day of the SFU period.

Any AEs or SAEs that are ongoing at the end of the 3-day Safety Follow-up period will be managed as described in Section 8.2.6.

9.7 Early Termination Procedures

When a subject is discontinued from the study, all early termination procedures as listed in Table 8 are performed unless the subject refuses to perform the assessments or the procedures have already been performed during that study day.

Table 8 Early Termination

Procedures	Additional Information
Venous blood sample	- Safety panel hematology and clinical chemistry
Spot urine sample	- Safety panel - Pregnancy test (female)
Vital signs	After ≥5 min in supine position
ECG	After ≥10 min in supine position
Spirometry	After ≥15 min in sitting position
Risks of smoking/advice on smoking cessation / THS briefing	
Concomitant disease/ concomitant medication	
AE/SAE	
IP events/ malfunctions/ misuse	If applicable
Discharge	

Abbreviations: AE = Adverse event; ECG = Electrocardiogram; SAE = Serious adverse event

10 Quality Control and Quality Assurance

10.1 Monitoring

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

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

The PI or designee(s) shall access medical records for the Monitor in order that entries in the CRFs may be verified. As part of his/her(their) responsibilities, the PI or designee(s) is(are) expected to ensure that the study adheres to GCP requirements [22].

An Investigator's meeting will be held prior to or in conjunction with the Site Initiation visit. During this meeting, the general training of the study procedures and specific training on selected procedures will be completed and documented.

In conjunction with, or after, the Investigator's meeting, and before the first subject is screened into the study, the Site Initiation visit will be conducted by the Monitor and, if necessary, together with the Sponsor or its authorized representative. The purpose of the Site Initiation visit is described in the Monitoring Plan.

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

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

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

Site visits will be made at regular intervals during the study. The frequency of the monitoring visits will be defined in the Monitoring Plan.

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

10.2 Training of Staff

A formal meeting (Investigator's meeting) will be conducted prior to or in conjunction with the Site Initiation visit. During this meeting, the requirements of the clinical study protocol and related documents will be discussed, and training to the relevant systems and other

study-specific procedures will be provided. The activities of this meeting will be described in the Monitoring Plan.

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

10.3 Audits and Inspections

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

Authorized representatives of the Sponsor, regulatory agencies and/or an IEC may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines [22], and any applicable regulatory requirements. The PI or designee(s) will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.

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

10.4 Risk Management

According to ICH-GCP E6(R2) Section 5, the sponsor will implement a system to manage quality throughout all stages of the study process. Pursuant to this, a risk management process will be implemented including identification and scoring of risks, identification of critical data and processes. Risk assessment log will be periodically reviewed during monthly meetings with the CROs.

This risk management approach will be described in the Risk Management Plan which will be developed during the set-up phase of the study and reviewed throughout all stages of the study.

In addition, at the end of study, the Sponsor will describe in the CSR the quality management approach implemented in the study.

11 Data Management Activities

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

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

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

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

11.1.2 Protocol Deviations

Protocol deviations are considered as deviations from the study procedures as defined in this document, including but not limited to, as any violation of inclusion/exclusion criteria, mis-randomizations, assessments not performed or performed outside the scheduled time windows, or use of drugs that are known to affect components of the “smokers’ health profile”.

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

Information from the source documents will represent the primary source of protocol deviations. Information following site monitoring and other manual reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual

review and will be recorded and tracked in the CTMS or other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, documented and tracked as protocol deviations, as necessary.

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

Subjects with major protocol deviations will be identified to determine whether they will be excluded from any of the analysis populations.

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

The categories for the major and minor deviations will include, but are not limited to the deviations presented in Table 9 and Table 10.

Table 9 Definition of Major Protocol Deviations Categories

Sub-Category	Description
Protocol violation	Violation of inclusion/exclusion criteria. Or missing documentation of any of the inclusion/exclusion criteria at time enrollment.
Procedural deviation	Deviation to any study procedures.
Mis-randomization	Misclassification of subject's sex at randomization. Or incorrect product administered according to randomized sequence.
Use of TNP not allowed	Use of any nicotine or tobacco–containing product other than the assigned product during the exposure period, or use of any nicotine tobacco-containing product during at least 23 hours of abstinence from any nicotine/tobacco containing products (nicotine wash-out).

Table 10 Definition of Minor Protocol Deviations Categories

Sub-Category	Description
Procedural deviation	Deviation to any study procedures.
Time deviation (Plasma nicotine PK sample)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Section 4.1)
Time deviation (other assessment)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Section 4.1)
Assessment missing (Plasma nicotine PK sample)	Assessment is missing
Assessment missing (other assessment)	Assessment is missing

11.1.3 Data Handling

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

Data of all subjects who sign the ICF, including screen failures, will be captured in the source documents.

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

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

Additional details are covered in the DMP.

12 Planned Statistical Methods

12.1 General Considerations

Full details of the statistical analysis will be provided in the Statistical Analysis Plan (SAP). The following statistical analyses will not be performed prior to the finalization of the SAP. Any changes to the planned statistical methods from the SAP will be documented in the clinical study report (CSR). The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

The sample randomization will enforce at least 40% of each sex (i.e., a minimum of 12 females and 12 males), therefore analyses will be stratified by sex (male and female), as well as unstratified, as detailed in the SAP.

12.1.2 Definitions for Statistical Data Analysis

For PK and PD analyses, baseline will be defined as the last assessment prior to T0 (5 minutes prior to T0 for blood sampling and 15 minutes for VAS questionnaires) for each study day of exposure.

Nicotine PK parameters (T_{max}, C_{max}, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}t'}$) will be derived from measured plasma nicotine concentrations-time data. Nicotine PK parameters will be derived from plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique. All PK parameters will be computed in measured plasma nicotine concentration-time. Indeed, due to the study requirement of at minimum 23 hours of nicotine abstinence before any IP use and the typical half-life of plasma nicotine of about 2 hours [23]. Then after 23 hours of nicotine abstinence it is expected that a maximum of 0.05% of nicotine will be present. Descriptive Statistics

All data will be presented in listings, ordered by subject, study visit, IP, and time point, unless otherwise specified.

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), 95% confidence interval (CI) of the arithmetic mean, median, first and third quartiles, minimum, maximum; for log-normal data, the geometric mean, geometric coefficient of variation (CV), and 95% CI of the geometric mean will be presented instead of arithmetic mean, SD, and 95% CI of the arithmetic mean, respectively.

For log normally distributed endpoints (C_{max}, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}t'}$), geometric mean, geometric CV, and confidence interval will be presented additionally.

Nominal categorical variables will be summarized by frequency statistics (number and percentage), including the number of missing data as a category.

Ordinal categorical data (e.g., T_{max}) will be summarized by number of subjects (n), number and percent of subjects with missing data, median, first and third quartiles, and minimum and maximum.

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

For PK and PD endpoints, all analyses and summaries will be performed by IP.

For safety endpoints, analyses and summaries will be performed by IP and sequence, and overall.

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

When applicable, the number and % of subjects with values below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will also be presented. If 50% or more data are below LLOQ or above ULOQ, only the number and percent of values below LLOQ or above ULOQ will be reported in the summaries, together with minimum (= LLOQ/2) and maximum (= ULOQ) of the observed values.

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

In general, missing data will not be imputed in this study, due to the nature of the measurements and the short periods of exposure and use. However, for questionnaire data, total scores and domain or subscale scores may use a certain degree of imputation by averaging across individual item scores. Further details will be provided in the SAP.

In general, bioanalytical values below the lower limit of quantification (LLOQ) will be imputed using 0.5 x lower limit of quantification. For values above the upper limit of quantification (ULOQ), the ULOQ will be used for calculation and reporting in summary tables.

For nicotine concentrations below the LLOQ (BLOQ):

- BLOQ values before T0 will be imputed by LLOQ/2
- BLOQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC)
- Any BLOQ value (after T0 and before the last quantifiable value) would need to be queried and, if confirmed, it will be imputed by LLOQ/2.

The number and percent of values below LLOQ or above ULOQ will be presented in each summary table.

12.1.4 Significance Level for Inferential Analysis

No significance level will be used. All confidence intervals will be computed at 95%.

12.2 Analysis Sets

Populations will be described based on the screened population.

Demographics, baseline characteristics, PK and PD endpoints, and amount of nicotine delivered, will be analysed using the randomized and PK population.

Safety will be analysed using the safety population.

12.2.1 Screened Population

The screened population consists of all subjects who underwent at least one screening procedure.

12.2.2 Safety Set (SAF)

The safety population is a subset of the screened population and consists of all subjects who give informed consent and have at least one safety assessment.

12.2.3 Randomized Population

The randomized population is a subset of the safety population and consists of all the subjects who were randomized at Baseline (Day -1). Subjects for which inclusion/exclusion criteria were violated or subject for which the documentation for eligibility was incomplete at time of enrolment will be excluded from this population.

12.2.4 Pharmacokinetics Population

The Pharmacokinetic (PK) Population is a subset of the randomized population and consists of all randomized subjects for whom at least one nicotine PK parameter can be derived. Only subjects without major protocol deviations, as defined in the SAP, which have an impact on evaluability of the main objective, as described in Section 3.1, will be included in the PK population.

12.3 Demographics and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the PK population. This summary will also be performed for the randomized population if there is at least a difference of 1 subject between the populations.

Summaries will include sex, age, height, weight, BMI, TNP use history, FTND score, and other endpoints that are only captured prior to product use.

These data will be summarized using the appropriate summary statistics.

12.4 Main Objective

12.4.1 Main Estimand Analysis

The main estimand related to the main objective is defined by the following components:

Product Use Under Evaluation:

- Single use of THS with either a regular or a menthol stick or of a single CIG

Target Population:

- Healthy adult smokers, who satisfy all eligibility criteria (see Section 5.1)

Variable(s) of Interest:

- Maximum nicotine plasma concentration [C_{max}]
- Time to the maximum nicotine plasma concentration [T_{max}]
- Area under the curve of nicotine plasma concentration-time computed from T0 to T=24 hours [$AUC_{0\text{-}24h}$]
- Area under the curve of nicotine plasma concentration-time computed from T0 to the subject-specific time of maximum nicotine concentration [$AUC_{0\text{-}t'}$]

C_{max}, T_{max}, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}t'}$ computed on observed plasma nicotine concentration-time curves.

Intercurrent Events:

- Subject's non-adherence with single IP use: If the subject uses other tobacco or nicotine product than the planned IP, or if the subject does not adhere with the planned single IP use, the variables of interest from the related sequence's period will be set to missing and handled as Missing at random (MAR).
- Subject's non-adherence with abstinence periods: If the subject has used any TNP during an abstinence period, the subject's variable of interest data from the related sequence's period will be set to missing and handled as MAR.
- Subject's discontinuation. The corresponding subject's variable of interest missing data will be handled as MAR.

Population-Level Summary Statistic:

- Geometric means ratios for C_{max}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}t'}$

12.4.1.1 Baseline Comparability

Not applicable.

12.4.1.2 Descriptive Analysis

Endpoints will be summarized using the randomized and the PK population.

12.4.1.3 Missing Data Strategy

See Section 12.1.3 for missing data strategy.

12.4.1.4 Main Analysis

A mixed model analysis of variance (ANOVA) will be conducted on $AUC_{0\text{-}24h}$, C_{max}, and $AUC_{0\text{-}t}$, endpoints in the natural logarithmic scale.

The model will include terms for sequence, period, product exposure as fixed effects and subject as a categorical random effect modeling the within subject correlations. The ANOVA analysis could be performed using the following SAS code:

```
PROC MIXED data=< > method=REML;
class subject sequence period product;
model log(parameter) = sequence period product/ddfm=KR;
repeated product / subject=subject type=csh;
lsmeans product / pdiff=control("CIG") cl alpha=0.05;
RUN;
```

The results of this analysis for each of are presented in terms of geometric least square ratios and 95% confidence intervals for the THS / CIG ratio.

This approach is consistent with the guidelines in the European Medicines Agency's guidelines for bioequivalence investigations [24] and FDA's Center for Drug Evaluation and Research [25].

The analysis of T_{max} will be performed by conducting a Wilcoxon signed rank test and calculating the median T_{max} for each product along with the Hodges-Lehmann [26] estimate of the median difference between products, and the related 95% CI. This analysis could be performed using the following SAS code:

```
PROC NPAR1WAY hl(refclass=<>) alpha=.05 data=<> hl;
  class TRT;
  var AVAL;
  ods output HodgesLehmann=HodgesLehmann;
RUN;
```

12.4.1.5 Sensitivity Analyses

In case of any uncorrected nicotine concentration at T0 [uC0] greater than 5% of their uncorrected maximum value, a sensitivity analysis of the PK endpoints will be performed similarly to the main analysis, whereby data of these subjects for this specific study day will be excluded from the analysis.

12.4.1.6 Supplementary Analysis

No supplementary analysis is foreseen.

12.5 Secondary Objectives

12.5.1 Secondary Objective 1

To evaluate pharmacodynamic (PD) effects (subjective effects) of a single use of a THS with either a regular or a menthol stick or of a single CIG. Endpoints will be analysed by investigational product (IP).

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% CI of mean) VAS *Craving* assessment, VAS *Liking* assessment, and VAS *Intention to Use Again* assessment will be provided by IP and assessment time point, when applicable. Change from baseline (pre-product use) for VAS *Craving* score will be summarized by study product and assessment time point. Individual responses will be listed. Summaries will be further stratified by sex.

12.5.2 Secondary Objective 2

This analysis refers to the secondary objective 2 defined in Section 3.2, which is to evaluate the safety of test products during the study.

In general, all safety data will be listed and tabulated. Safety variables collected during exposure periods will also be reported by randomization sequence.

AE data will serve for the assessment of safety. Other safety variables monitored in this study will include the incidence of THS product events including malfunction/misuse; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; clinical chemistry, hematology, and urine analysis safety panel; physical examination; concomitant medication.

The number and percentage of subjects with AEs, SAEs, and IP events will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to discontinuation, AEs leading to death, AEs by relatedness to product exposure, AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

Safety laboratory assessments are performed on Day -1 and Day 3 in the morning prior to product use (Appendix A). Any lab related AEs on Day 3 will be assigned to the product used on the previous day.

Summary tables showing actual values and change from baseline of clinical findings will be provided for spirometry, ECGs, vital signs, and laboratory parameter. Descriptive statistics will be summarized by study day for ECG, vital signs and for laboratory parameters.

12.6 Interim Analysis

No interim analysis is foreseen in this study.

12.7 Measures to Control Bias

12.7.1 Blinding

A certain level of blinding, for study statisticians and study scientists (CRO personnel which will be author of the body SAP), will be required before the body SAP, document describing all the analysis, will be finalized, and signed.

Table 11 Blinding Scheme

Blinded Study Personnel	End of Blinding Period
PMP and CRO Study Statisticians	After the SAP finalization. Can be actively un-blinded when appropriate.
PMP and CRO Clinical Scientist	After the SAP finalization. Can be actively un-blinded when appropriate.

12.7.2 Multiple Testing Procedures

Not applicable.

12.7.3 Determination of Sample Size and Power Consideration

In this study 30 subjects will be randomized to 6 product use sequences, i.e., all full crossover sequences for three investigational products (THS regular, THS menthol and CIG). This sample size is empirically based as there are no considerations for statistical hypothesis.

In an analysis of confidence interval precision on the THS / CIG C_{max} ratios, performed with SAS 9.4 using 10,000 simulations.

The precision of C_{max} ratios has been determined to be of 0.191 or less.

12.7.3.1 Assumptions

The precision has been determined using the following geometric mean (GeoM), geometric coefficient of variation (GCV) and within subject correlation assumptions for C_{max}:

- The GeoM of C_{max} is assumed to be 10, 12, 14 ng/mL for THS menthol, THS regular and CIG respectively with a common GSD of 0.8. These are derived from the following study results.

Study	ZRHM-PK-06-US		ZRHM-PK-05-JP		ZRHR-PK-01-EU		ZRHR-PK-02-JP	
Product	THS	CIG	THS	CIG	THS	CIG	THS	CIG
GeoMean (Stat Desc)	7.4	13.8	10.7	12.09	9.62	12.42	14.3	13.82
GeoCV % (Stat Desc)	99.83	97.35	171.0	87.71	84.26	56.13	82.82	84.00

12.7.3.2 Method

The analysis of confidence interval precision on the THS / CIG C_{max} ratios has been implemented using SAS version 9.4, simulating 10000 sets of log-transformed data for 30 subjects with the assumptions described in section 12.7.3.1, and the 6 sequences of this full cross-over design.

The statistical analysis has been performed with a linear model with repeated measurement including as fixed effect the sequence, the period, and the product exposure.

The THS / CIG C_{max} ratios and related confidence intervals have been determined by using the exponential of the difference between THS variants and CIG on the log-transformed data.

Then precision has been determined as the 90^{th} percentile of the 95% confidence interval of the THS / CIG C_{max} ratios.

13 Administrative Considerations

13.1 Study Administrative Structure

13.1.1 Sponsor

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

13.1.2 List of Principal Investigators and Sites

The list of principal investigators and sites will be provided as a separate document.

13.2 Subject Confidentiality

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

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

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

13.3 Access to Source Documents

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

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

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans, ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study, and the actions taken will be maintained by the Investigator/study site for the study, as required by ICH GCP [22] and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in Section 8 of the ICH Tripartite Guideline for Good Clinical Practice [22].

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

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

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

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

- Signed informed consent documents for all subjects and master ICF.
- Subject identification code list, screening log, and enrollment log (if applicable).
- Record of all communications between the Investigator and the IEC, composition of the IEC.
- Record of all communications/contact between the PI(s) or designee(s), Sponsor, and its authorized representatives.
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curricula vitae, and their signatures.
- Investigator logs.
- CRFs, study specific questionnaires (and associated data/scoring), subject diaries.

- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (e.g., ECGs, consultation reports, physical examination, laboratory records) or any electronically captured study source data.
- Clinical laboratory reports, laboratory normal ranges.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).
- Record of any body fluids or tissue samples collected and retained.
- Device issue log, IP accountability logs, dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

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

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

If the PI wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

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

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

13.5 Clinical Study Report

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

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

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

13.6 Financial Disclosure

The PI is required to provide financial disclosure information to the Sponsor. In addition, the PI must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year following the completion of the study.

13.7 Publication and Disclosure Policy

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

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

13.8 Insurance

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

14 Reference List

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Appendices

Appendix A Schedule of Events

Study Assessments

	Screening	Baseline	Exposure				Safety Follow-up
Visit	**1**	**2**				**Early Termination**	**Phone contact**
Study Day (D)	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**		**+ 3 Days**
Informed consent	●						
FTND	●						
Information on risks of smoking, smoking cessation advice, and briefing on THS	●	●			●	●	
TNP use history questionnaire	●	●					
Inclusion/exclusion criteria	●	●					
ECG	●	●			●	●	
Spirometry	●	●			●	●	
Demographics	●						
Medical history	●						
Concomitant diseases and medication	●	●	●	●	●	●	
Physical examination	●						
Body height, body weight, BMI	●						
Vital signs	●	●	●	●	●	●	
B: HIV, HBV, and HCV	●						
Identification of CIG brand	●						

	Screening	Baseline	Exposure				Safety Follow-up
Visit	**1**	**2**				**Early Termination**	**Phone contact**
Study Day (D)	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**		**+ 3 Days**
U: Drug screen	●	●					
U: Cotinine test	●	●					
U: Pregnancy test	●	●			●	●	
Alcohol breath test	●	●					
B & U: Safety laboratory panel (non-fasting Day 3 + ET)	●	●			●	●	
THS demonstration (without use)	●						
Randomization		●					
IP use (THS or CIG)			●	●	●		
B: plasma nicotine samples			●	●	●		
VAS *Craving* assessment			●	●	●		
VAS *Liking* assessment			●	●	●		
VAS *Intention to Use Again* assessment			●	●	●		
AE/SAE recording	●	●	●	●	●	●	●
Product events, malfunctions, misuse			●	●	●	●	
Phone call at end of SFU period							●

Abbreviations:

AE = Adverse event; B: Blood sample required; BMI = Body mass index; CIG = Combustible cigarette(s); ECG = Electrocardiogram; ET = Early termination; FTND = Fagerstroem test for nicotine dependence; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; SAE = Serious adverse event; THS = Tobacco Heating System; U = Urine sample required; VAS = Visual analog scale

Appendix B Participating Laboratories

Safety Laboratory

[redacted]

Bioanalytical Laboratory

[redacted]

Appendix C 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 points]; Moderate [4 – 6 points]; Severe [7 – 10 points].

Appendix D Questionnaire scoring rules

VAS *Craving* Assessment

Cigarette craving will be evaluated using a one-item self-reported VAS *Craving* assessment [14], asking subjects to rate craving for cigarettes (*How strong is your craving for cigarettes?*), on a 100 mm unipolar scale, ranging from 0 (no craving) to 100 (strong craving).

Prior to T0

- T_V0: within 15 minutes prior to T0

After T0

- T_V1 after 4 minutes (± 2 minutes)
- T_V2 after 10 minutes (± 2 minutes)
- T_V3 after 15 minutes (± 2 minutes)
- T_V4 after 30 minutes (± 2 minutes)
- T_V5 after 10 hours (± 5 minutes)

VAS *Liking* Assessment

Liking will be evaluated using a one-item self-reported VAS *Liking* assessment, asking subjects to rate liking for the product (*Overall, my liking for this product is:*) on a 100 mm bipolar scale, ranging from 0 (strong disliking) to 100 (strong liking), with a neutral middle point, as recommended in the FDA guidance for industry on abuse liability assessment [15].

- Tv3 after 15 minutes (± 1 minute)

VAS Intention to Use Again Assessment

Intention to use the product again will be evaluated using a one-item self-reported VAS [16], asking subjects to rate intention to use product again *(How likely are you to use this product again)* on a 100 mm bipolar scale, ranging from 0 (very unlikely) to 100 (very likely), with a neutral middle point.

- Tv3 after 15 minutes (± 1 minute)

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