PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

ZRHM-PK-06-US

Study title:	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine nasal spray
Short name:	Nicotine pharmacokinetic profile and safety of THS 2.2 Menthol
Registration number:	Not assigned
Product name:	Tobacco Heating System 2.2 Menthol
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	Final
Date:	22 May 2013
Authors:	[redacted], PhD, Manager Clinical Science [redacted] PhD, Biostatistician [redacted], MD, Medical Safety Officer [redacted] Medical Writer

SYNOPSIS

Sponsor:

Philip Morris Products S.A.

Name of Product:

Tobacco Heating System 2.2 Menthol

Study Title:

A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine nasal spray

Short Study Title:

Nicotine pharmacokinetic profile and safety of THS 2.2 Menthol

Study Number and Acronym:

ZRHM-PK-06-US, no acronym

Primary Objective:

To evaluate the rate and the amount of nicotine absorbed (as assessed by maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC] from start of product use to time of last quantifiable concentration [$AUC_{(0\text{-last})}$]) from THS 2.2 Menthol relative to menthol conventional cigarettes (mCC), following single use of THS 2.2 Menthol and mCC.

Secondary Objectives:

- To determine if C_{max} and $AUC_{(0\text{-last})}$ of the THS 2.2 Menthol are higher relative to nicotine nasal spray (NNS) following single use of the THS 2.2 Menthol and NNS.
- To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to time of last quantifiable concentration to infinity [$AUC_{(0\text{-}\infty)}$] and partial AUC, where t' is the subject-specific time of maximum nicotine concentration following single use of the mCC or NNS product [$AUC_{(0\text{-}t')}$]) between the THS 2.2 Menthol and mCC, as well as the THS 2.2 Menthol and NNS.
- To evaluate the time to the maximum concentration (t_{max}) of nicotine for the THS 2.2 Menthol as compared to mCC and to determine if the t_{max} for THS 2.2 Menthol is shorter as compared to NNS.
- To describe the terminal half-life ($t_{1/2}$) of nicotine for the THS 2.2 Menthol, mCC, and NNS.

- To describe the differences on urge-to-smoke over time between the THS 2.2 Menthol and mCC, as well as between the THS 2.2 Menthol and NNS.
- To describe product evaluation in the THS 2.2 Menthol and mCC users.
- To describe the levels of carbon monoxide (CO) exposure for the THS 2.2 Menthol, as compared to mCC and NNS users.
- To describe the plasma levels of cotinine in the THS 2.2 Menthol, mCC, and NNS.
- To monitor the safety during the study.

Primary Endpoints:

- Primary nicotine PK parameters (THS 2.2 Menthol vs. mCC):
  - $C_{max.}$
  - $AUC_{(0\text{-}last).}$

Evaluation criterion: The study will be considered successful if the 95% Confidence Intervals (CI) of the THS 2.2 Menthol:mCC ratio for the primary nicotine PK parameters are estimated with a precision of ±20%.

Secondary Endpoints:

- Primary nicotine PK parameters (THS 2.2 Menthol vs. NNS).
- Secondary nicotine PK parameters
  - $AUC_{(0\text{-}\infty)}$.
  - Partial $AUC_{(0\text{-}t')}$.
  - $t_{max.}$
  - $t_{1/2}$
- Subjective smoking effects:
  - Urge-to-smoke questionnaire (Questionnaire of Smoking Urges brief [QSU-brief]).
  - Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]).
- CO exposure biomarkers: levels of exhaled CO and carboxyhemoglobin (COHb) in blood.
- Cotinine levels in plasma prior $T_{0,}$ $T_{0 + 12 \text{ hours}}$ (T_{14}), $T_{0 + 24 \text{ hours}}$ (T_{15}).
- Safety variables:
  - Incidence of adverse events (AEs)/serious adverse events (SAEs) including THS 2.2 Menthol malfunction/misuse.
  - Respiratory symptoms: cough assessment by visual analogue and Likert scales and one open question.
  - Vital signs.

- Spirometry.
- Electrocardiogram (ECG).
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medication.

Additional Study Assessments:

- Serology for human immunodeficiency virus 1/2 and Hepatitis B and C.
- Urine pregnancy test (females only), urine cotinine test, urine drug screen.
- Alcohol breath test.
- Chest X-ray.
- Nicotine dependence to be assessed with the Fagerström Test for Nicotine Dependence revised version.
- Socio-economic status questionnaire.
- Cytochrome P450 2A6 (CYP2A6) activity (nicotine metabolic molar ratio) in plasma.

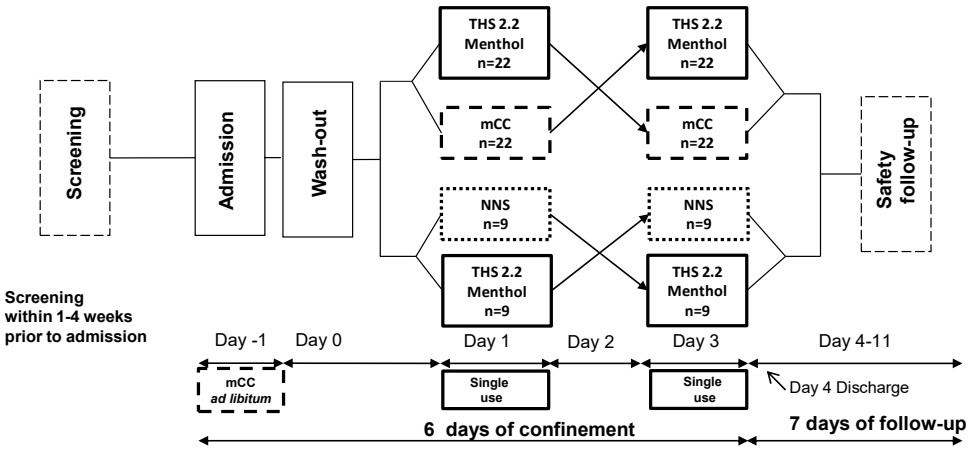
Study Design:

This is a randomized, controlled, 2-period, 4-sequence, single-use crossover study. An incomplete block design is adopted, where each subject will receive only two of the three products (Figure S1):

- THS 2.2 Menthol.
- mCC.
- NNS.

Figure S1: Study Flowchart

- Cross over with incomplete block design, 4 sequences
- 62 smokers to be randomized



THS: Tobacco Heating System; *mCC*: menthol conventional cigarette(s); *NNS*: nicotine nasal spray

Subjects will be admitted to the clinic on Day -1. The confinement period will then consist of 2 periods (Period 1, Period 2) with each period consisting of at least 24-hour nicotine wash-out (nicotine abstinence) and 1 day of single product use.

Period 1: Day 0: Wash-out; Day 1: single product use (THS 2.2 Menthol/mCC/NNS)

Period 2: Day 2: Wash-out; Day 3: single product use (THS 2.2 Menthol/mCC/NNS).

In total, 62 eligible, healthy smoking subjects will be randomized to one of 4 sequences:

Sequence 1:	THS 2.2 Menthol	→	mCC (N=22)
Sequence 2:	mCC	→	THS 2.2 Menthol (N=22)
Sequence 3:	THS 2.2 Menthol	→	NNS (N=9)
Sequence 4:	NNS	→	THS 2.2 Menthol (N=9)

Subjects will be discharged (time of discharge) from the investigational site in the morning of

Day 4 after performance of the Day of Discharge assessments.

From the time of discharge until Day 11: A 7-day safety follow-up will be done for the recording of spontaneously reported new AEs and SAEs, and the active follow-up of ongoing AEs/SAEs by the site.

Study Population and Main Criteria for Inclusion:

A total of 62 smoking, healthy adult subjects without any restriction to races and ethnicities, meeting the following main inclusion criteria:

- Subject is aged from 22 to 65 years (inclusive).
- Smoking, healthy subject as judged by the Investigator.
- Subject smokes at least 10 commercially available mCCs per day of the following brands: Kool mild, Kool, Newport Menthol Short, Newport Menthol, Newport Menthol 100, Camel menthol silver, Camel menthol, Marlboro Menthol and sub-brands) for the last 4 weeks, based on self-reporting.
- Subject does not plan to quit smoking in the next 3 months.
- The subject is ready to accept interruptions to smoking for up to 4 days.
- The subject is ready to accept using the THS 2.2 Menthol and the NNS product.

Subjects will be randomized to 1 of 4 sequences. Each sex and each of the smoking strata (International Organization for Standardization [ISO] nicotine levels ≤1 mg and >1 mg) will have a quota applied to ensure they represent at least 40% of the study population for each of the Group-1 and Group-2.

Subjects who do not complete the study after randomization will not be replaced.

Investigational Products

- Test Product: Tobacco Heating System 2.2 Menthol
- Reference Product: Subject's own supply of commercially available preferred single brand mCC.

Reference Point Product (non-investigational): Nicotine Nasal Spray (Nicotrol®NS 10 mg/mL); 1 spray (resulting in the administration of 0.5 mg nicotine) per nostril/product use, as per label. This will be not supplied by the Sponsor.

Duration of Study:

The entire study per subject will last 14 to 41 days, including a Screening period of up to 4 weeks prior to Admission (Day -29 to Day -2), 6 days of confinement (Day -1 to time of discharge on Day 4), and 7 days of safety follow-up (from time of discharge until Day 11).

Statistical Methods:

All primary and secondary endpoints will be summarized with descriptive statistics. In addition, PK, subjective effects of smoking, and safety variables will be analyzed as follows.

Pharmacokinetics: the analysis populations for the PK endpoints will be composed of two analysis sets to allow the comparison between THS 2.2 Menthol and NNS separately from the comparison between THS 2.2 Menthol and mCC. Only subjects without major protocol deviations will be included in the PK analysis sets.

Nicotine PK parameters will be derived from plasma nicotine versus time data using a non-compartmental technique.

An analysis of variance (ANOVA) will be conducted on logarithmically transformed $AUC_{(0\text{-}last)}$ and C_{max} primary endpoints. The model will include terms for sequence, subjects within sequence, period, and exposure group as fixed effect factors. The results of this analysis for each of $AUC_{(0\text{-}last)}$ and C_{max} will be presented in terms of adjusted geometric least square means and 95% confidence intervals (CI) for the THS 2.2 Menthol:CC and THS 2.2 Menthol:NNS ratios. The lower bound of the 95% CI of the THS 2.2 Menthol:NNS ratio for C_{max} and $AUC_{(0\text{-}last)}$ will be compared with 1.00, to determine if the rate and the amount of nicotine absorbed of the THS 2.2 Menthol are higher relative to NNS.

$AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}t')}$, and $t_{1/2}$ will be analyzed using the same approach adopted for the primary endpoints. The one-sided Wilcoxon Signed-Rank Test (α=0.025) will be used to test if the t_{max} in THS 2.2 Menthol is shorter than in NNS. The median t_{max} differences between THS 2.2 Menthol and mCC as well as between THS 2.2 Menthol and NNS, will be presented together with Hodges-Lehmann estimates of the 95% CI.

Subjective effects of smoking: mixed effects ANOVA using period, sequence, and product exposure as fixed effects and subjects within sequence as random effects will be adopted to analyze the domain scores of the product evaluation (MCEQ) questionnaire, for the comparison between THS 2.2 Menthol and mCC. The same model will be evaluated for the analysis of cotinine and Urge-to-smoke (QSU-brief), including the assessment time points as repeated measurements. The results will be presented in terms of least square means and 95% CI for the THS 2.2 Menthol-mCC and THS 2.2 Menthol-NNS differences.

Cotinine levels will be summarized by means of descriptive statistics reported by exposure.

Safety: The safety population will comprise all subjects, who are exposed to THS 2.2 Menthol during the study, including the product test at admission. Adverse event data will serve as the primary assessment of safety. All safety data will be listed and tabulated by sequence and by product use.

Sample Size:

A total of 62 subjects will be randomized. This is calculated by adding up sample sizes separately estimated for each analysis.

A total of 44 subjects are needed to estimate the mean C_{max} parameter ratio between THS 2.2 Menthol and mCC with a 90% probability of obtaining a margin of error (95% CI) of at most ±20%, assuming that THS 2.2 Menthol have a nicotine PK profile similar to mCC (C_{max} ratio equal to 1.00) and a 10% dropout rate.

A total of 18 subjects are needed to estimate the mean C_{max} parameter ratio between THS 2.2 Menthol and NNS with a precision allowing for the lower bound of the 95% CI exceeding 1.00, with 90% power and assuming a 10% dropout rate. The anticipated geometrical C_{max} ratio between THS 2.2 Menthol and NNS is 1.55.

The sample size of this study is based on our current understanding of THS 2.1 non-menthol, the previous prototype of THS 2.2 Menthol, where the within-subject coefficient of variation for nicotine C_{max} and $AUC_{(0\text{-last})}$ was found to be approximately equal to 36% and 21%, respectively.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADL	Activities of daily living
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time 0 extrapolated to time of last quantifiable concentration to infinity
$AUC_{(0\text{-last})}$	Area under the concentration-time curve from T_0 to time of last quantifiable concentration
$AUC_{(0\text{-t'})}$	Partial AUC, where t' is the subject-specific time of maximum nicotine concentration following the single use of conventional cigarettes or nicotine nasal spray
BMI	Body mass index
CC	Conventional cigarette(s). The menthol CC are referred as mCC.
CD	Compact Disc
CFR	Code of Federal Regulations
CI	Confidence interval
Clast	Last quantifiable concentration
C_{max}	Maximum concentration
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CTMS	Clinical Trial Management System
CV (documentation)	Curriculum vitae
CV (statistics)	Coefficient of variation
CYP2A6	Cytochrome P450 2A6

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End-of-Study Visit
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
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MRTP	Modified risk tobacco product
NNS	Nicotine nasal spray
NRT	Nicotine replacement therapy
PK	Pharmacokinetic(s)
PMI	Philip Morris International
QC	Quality control
QSU-brief	Questionnaire of Smoking Urges
SAE	Serious adverse event

SAP	Statistical analysis plan
SES	Socio-economic status
SHM	Sample handling manual
SOP	Standard Operating Procedure
T	Time point
T_0	Time point of first product use during study day
$t_{½}$	Half-life
THS	Tobacco Heating System
t_{max}	Time to maximum concentration
[redacted]	[redacted]
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual Analogue Scale
WBC	White blood cell (count)
WHO	World Health Organization
λz	Terminal elimination rate constant

Explanation of Terms

The following special terms are used in this protocol:

Charger	The function of the Charger (Model 4) is to recharge the Holder after use. It contains a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around, and can itself be recharged from a main power source.
Day of Discharge	Day 4.
End of Study	End of Study is defined as the last day of the 7 day safety follow-up subsequent to discharge from the unit.
Enrolment	On Day -1 for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed met and the subjects is willing and ready to use both the THS 2.2 Menthol and

	NNS (the test of both THS 2.2 Menthol and NNS are the last assessments prior to enrolment).
First product use time point	Start of product use for THS 2.2 Menthol is defined as the time of the first puff. The start time for mCC corresponds to the lighting of the mCC, and the start time of the NNS product is the time of the spray in the first nostril.
mCC	The term 'menthol conventional cigarette' refers to manufactured and commercially available menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Randomization	Assignment to product on Day 0 utilizing an Interactive Web and Voice Response System.
Safety follow-up	After the time of discharge, a 7-day safety follow-up will be done for the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site. In general any AE will be actively followed up until resolved, stabilized i.e. no worsening of the event or a plausible explanation for the event has been found.
Screening failure	Subjects who do not meet the entry criteria from ICF signature to the time of enrolment will be considered a screening failure and will be replaced by other subjects.
THS Menthol Tobacco Sticks (Menthol Tobacco Sticks)	The Menthol Tobacco Stick (product code C3 Menthol) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder.
THS Tobacco Stick Holder (Holder)	The function of the Holder (Model 4.2) is to heat the Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick).
Time of Discharge	Time when the subject is released form the site after all the procedures of the day of discharge have been conducted.
Tobacco Heating Device	The Device comprises everything in THS 2.2 Menthol except the Menthol Tobacco Stick.

Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)	THS 2.2 Menthol comprises the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable.

1. ETHICS AND REGULATIONS

1.1 Institutional Review Board Approval

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

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

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

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

These requirements for approval should in no way prevent any action from being taken by the Investigator or by the Sponsor in order to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the Investigator, and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately.

Relevant safety information will be submitted to the IRB during the course of the study in accordance with national regulations and requirements.

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, 2008 and are consistent with ICH/GCP applicable regulatory principles.

The Investigator agrees to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IRB. The Principal Investigator and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki, 2008 should be located in the Investigator's Study File.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form/Subject Information Sheet

At the Screening Visit, the Investigator or person designated by the Investigator will ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study, and the Investigator or the designee 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 discontinue his/her participation at any time. Once the subject has received all necessary information, and if he/she agrees to participate, this will be documented in the ICF/subject information sheet by the date and signature of both the subject and the person who conducted the informed consent discussion. No study-specific procedures will be performed before the ICF/subject information sheet has been signed.

The original, dated, and signed ICF(s)/subject information sheets must be kept in the Investigator study file at the site, and a copy must be given to the subject.

If a protocol amendment is required, or if new information regarding the risk profile of the Investigational Product (IP) becomes available, an amendment to the ICF/subject information sheet may be required. If revision of the ICF/subject information sheet is necessary, the Investigator will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IRB before subjects are required to re-sign the ICF/subject information sheet.

The subject will be informed that additional data analysis not mentioned in the protocol or the Statistical Analysis Plan (SAP) might be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by the principles of the ICH guidelines on GCP. These guidelines apply specifically to pharmaceutical development but nevertheless provide a robust and ethical framework for conducting clinical studies of tobacco products.

In addition, the Investigator will carry out the clinical study in accordance with applicable national and local laws of the pertinent regulatory authorities.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette smoking causes pulmonary and cardiovascular diseases and other serious diseases in smokers (U.S. Department of Health and Human Services, 2010). There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers cannot refrain from smoking or decide to continue smoking. To those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases. These products are now referred by the United States Food and Drug Administration (FDA) as modified risk tobacco products (MRTPs) (FDA, 2012a).

The challenge in developing and commercializing MRTPs is two-fold, i.e., developing tobacco products that are shown to reduce risk and are acceptable to smokers as substitutes for conventional cigarette(s) (CC). PMI is developing candidate MRTPs that provide an inhalation experience without combustion. The novel approach to achieve this is by heating tobacco at significantly lower temperatures than for CC.

PMI's approach to scientifically assessing the risk-reduction potential of its candidate MRTPs is described in the reference document (PMI White Paper Docket). Smoking cessation is the only intervention proven to reduce the risk of smoking-related diseases in smokers. Accordingly, PMI utilizes smoking cessation/smoking abstinence as the benchmark for assessing the risk reduction potential of its candidate MRTPs. The Institute of Medicine observed that cessation is the "gold standard" for assessing risk reduction, and that "the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit" (Institute of Medicine, 2012). PMI has already conducted studies and plans to conduct further clinical studies which observe measurable changes in blood chemistry, risk factors, and health effects in smokers who switch to a candidate MRTP, comparing the changes with those observed in both smokers who continue smoking CC and smokers who stop using tobacco products. Longer-term data from adults who continue to use the candidate MRTP can further substantiate reductions in individual risk in smokers and population harm.

2.1.2 Description of the Product and Scientific Findings

Thousands of chemicals — "smoke constituents" — are formed when tobacco is burned or combusted. More than 5,300 smoke constituents have been identified (Rodgman and Perfetti,

2009), and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) (FDA, 2011).

PMI's focus has been the development of products that do not combust tobacco but which replicate the "smoking experience" as much as possible. Our approach limits pyrolysis and combustion, by heating tobacco at significantly lower temperatures than CC. PMI believes that such products present the best opportunity for reducing harm because they produce vastly lower levels of harmful smoke constituents and are more likely to be accepted by smokers as substitutes for cigarettes. Important to this effort has been providing nicotine in a way that closely parallels CC.

The product developed by PMI, and to be assessed in this study, is the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). This product will be assessed in current smokers of menthol CC. With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for mCC, which can reach 900°C. The THS 2.2 Menthol is composed of the tobacco heating device, referred to as the 'THS Tobacco Stick Holder,' dedicated special Menthol Tobacco Sticks made of conventional tobacco, and different accessories. The energy of the THS Tobacco Stick Holder is sufficient to maintain approximately a 6 minute session. Unlike mCC, the Menthol Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of earlier development of THS 2.2 Menthol supports the initiation of the clinical studies described in this investigator's brochure (PMI, 2013a). No new or increased toxicological hazard in the product's aerosol was detected compared with CC smoke. The aerosol was chemically analyzed confirming that none of the determined HPHCs in the THS 2.2 Menthol were increased compared to the conventional cigarettes. The biological activity was tested in a number of *in vitro* assays to assess the cytotoxicity and the genotoxicity of the aerosol fractions total particulate matter (TPM) and gas vapor phase (GVP). In vitro and in vivo results corroborated the concept that absence of combustion when consuming tobacco substantially lowers toxic effects seen in these biological models. Further details on the clinical data are provided in the Investigators' Brochure (PMI, 2013a).

Several clinical studies have been conducted on THS 1.0 and THS 1.0 Menthol, an earlier development version of THS 2.2, in Europe, Asia, Africa and the United States. All studies showed reductions in exposure to the majority of measured HPHCs from both aerosol fractions, TPM and GVP, in subjects who used the THS 1.0 as compared to subjects continuing smoking CC, both, in controlled and ambulatory conditions. No clinical studies were conducted with THS 2.2 Menthol.

THS 2.1 non-Menthol was tested in two exploratory clinical studies to measure the nicotine plasma kinetic profile (PK) (clinical trial.gov identifier: NCT 01780688) and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1 (clinical trial.gov

identifier: NCT 01780714). The observed nicotine plasma PK profile for THS 2.1 was similar to CC as well, there were significant reductions in the exposure to the majority of selected HPHCs (PMI, 2013a).

Clinical studies conducted so far revealed no safety concern for either of the previous version of THS 2.2 Menthol tested.

2.2 Purpose of the Study

The purpose of this clinical study is to compare the profile of nicotine uptake (rate and extent of nicotine absorbed) after single use of THS 2.2 Menthol and menthol conventional cigarette (mCC) in healthy smokers. THS 2.2 Menthol will also be compared with the nicotine nasal spray (NNS) product, used as a reference point.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

According to a report from centers for disease control and prevention on quitting smoking among adults in US, 68.8% of current adult smokers report that they want to quit completely (

CDC, **2011**). Despite associated health risks, however, only 6.2% quit smoking successfully. Advice on health risks associated with smoking and smoking cessation advice will be provided on Screening, on Admission, on Day 4 (Day of Discharge). The advice will follow the recommendations of the U.S. Public Health Service (U.S. Public Health Service, 2008). Subjects who are motivated to quit smoking during the study will be given the opportunity to continue their smoking cessation attempt and will be referred to appropriate stop smoking services for continuing support and counseling at a higher level. Subjects who participate in this study will also benefit from repeated, detailed health check-ups, which may help to uncover undiagnosed medical conditions.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

- Risks related to blood sampling, e.g., excessive bleeding, fainting, hematoma, paresthesia, or infection, and amount of blood taken over a period of time.
- Risks related to chest X-rays, e.g., a small increase of risk to develop cancer later in life.
- Risks related to drug application as part of testing procedures (i.e., spirometry with short-acting bronchodilator at Screening) per study protocol and scientifically accepted standards.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product (THS 2.2 Menthol) or Reference Point Product

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

- Risks specific to the use of any NNS, as per the relevant summary of product characteristics.

All risks related to study procedures, IP, reference product, or support for smoking abstinence will be explained in detail to the subjects. Mitigation will include, but will not be limited to:

- Close monitoring and medical evaluation of potential safety signals throughout the study and follow-up.

- Using accepted research and scientific standards (e.g., blood samples not to exceed blood donation standards).Management and follow-up of adverse events (AEs)/serious adverse events (SAEs).

2.3.4 Unforeseeable Risks

As with any IP, reference product or smoking abstinence, there may be unforeseeable risks and hazards that could occur. The possibility of such will be explained at Screening, Admission, and Day of Discharge. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest possibility.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To evaluate the rate and the amount of nicotine absorbed (as assessed by maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC] from start of product use to time of last quantifiable concentration [$AUC_{(0\text{-}last)}$]) from THS 2.2 Menthol relative to mCC, following single use of THS 2.2 Menthol and mCC.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To determine if C_{max} and $AUC_{(0\text{-}last)}$ of the THS 2.2 Menthol are higher relative to NNS following single use of the THS 2.2 Menthol and NNS.
- To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to time of last quantifiable concentration to infinity [$AUC_{(0\text{-}\infty)}$] and partial AUC, where t' is the subject-specific time of maximum nicotine concentration following single use of the mCC or NNS product [$AUC_{(0\text{-}t')}$]) between the THS 2.2 Menthol and mCC, as well as the THS 2.2 Menthol and NNS.
- To evaluate the time to the maximum concentration (t_{max}) of nicotine for the THS 2.2 Menthol as compared to mCC and to determine if the t_{max} for THS 2.2 Menthol is shorter as compared to NNS.
- To describe the terminal half-life ($t_{1/2}$) of nicotine for the THS 2.2 Menthol, mCC, and NNS.
- To describe the differences on urge-to-smoke over time between the THS 2.2 Menthol and mCC, as well as between the THS 2.2 Menthol and NNS.
- To describe product evaluation in the THS 2.2 Menthol and mCC users.
- To describe the levels of carbon monoxide (CO) exposure for the THS 2.2 Menthol, as compared to mCC and NNS users.
- To describe the plasma levels of cotinine in the THS 2.2 Menthol, mCC, and NNS.
- To monitor the safety during the study.

3.3 Primary Endpoints

- Primary nicotine PK parameters (THS 2.2 Menthol vs mCC):
  - $C_{max.}$
  - $AUC_{(0\text{-}last).}$

Evaluation criterion: The study will be considered successful if the 95% Confidence Intervals (CI) of the THS 2.2 Menthol:mCC ratio for the primary nicotine PK parameters are estimated with a precision of ±20%.

3.4 Secondary Endpoints

- Primary nicotine PK parameters (THS 2.2 Menthol vs NNS).
- Secondary nicotine PK parameters:
  - $AUC_{(0\text{-}\infty)}$.
  - Partial $AUC_{(0\text{-}t')}$.
  - $t_{max.}$
  - $t_{1/2}$
- Subjective smoking effects:
  - Urge-to-smoke questionnaire (Questionnaire of Smoking Urges brief [QSU-brief]).
  - Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]).
- Carbon monoxide (CO) exposure biomarkers: levels of exhaled CO and carboxyhemoglobin (COHb) in blood.
- Cotinine levels in plasma prior $T_{0,}$ $T_{0 + 12\ hours}$ (T_{14}), $T_{0 + 24\ hours}$ (T_{15}).
- Safety variables:
  - Incidence of adverse events (AEs)/serious adverse events (SAEs) and device events including THS 2.2 Menthol malfunction/misuse.
  - Respiratory symptoms: cough assessment by visual analogue and Likert scales and one open question.
  - Vital signs.
  - Spirometry.
  - Electrocardiogram (ECG).

- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medication.

Additional Study Assessments:

- Serology for human immunodeficiency virus 1/2 and Hepatitis B and C.
- Urine pregnancy test (females only), urine cotinine test, urine drug screen.
- Alcohol breath test.
- Chest X-ray.
- Nicotine dependence to be assessed with the Fagerström Test for Nicotine Dependence revised version.
- Socio-economic questionnaire
- Cytochrome P450 2A6 (CYP2A6) activity (nicotine metabolic molar ratio) in plasma.

3.5 Exploratory Endpoints

There are no exploratory analyses planned.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, controlled, 2-period, 4-sequence, single use crossover study where each subject will receive two of the three products:

- THS 2.2 Menthol.
- mCC.
- NNS.

A Screening Visit will be conducted within 4 weeks prior to Admission to the investigational site (Day -29 to Day -2). A demonstration of the THS 2.2 Menthol and NNS will also be done by the site staff during the Screening Visit. Screening procedures do not necessarily have to be conducted on the same day. Subjects will be admitted to the clinic on Day -1 (Admission). On Day -1, as the last procedure of the eligibility assessments on that day, all subjects will undergo a product test: first for the THS 2.2 Menthol (using up to three Menthol Tobacco Sticks) and subsequently for NNS (1 spray of 0.5 mg per nostril as per label) prior to enrolment at Admission. In female subjects, the urine pregnancy test must be negative before any product test is performed (both the THS 2.2 Menthol and NNS). After all requested inclusion and exclusion criteria have been satisfactorily met, only subjects willing and ready to use both the THS 2.2 Menthol and NNS can be enrolled in order to minimize the drop-out rate during the course of the study.

The confinement period will consist of 2 periods (Period 1, Period 2) with each period consisting of a nicotine wash-out period (24 hours nicotine abstinence minimum) and 1 day of single product use.

Period 1: Day 0: Wash-out; Day 1: single product use (THS 2.2 Menthol/mCC/NNS).

Period 2: Day 2: Wash-out; Day 3: single product use (THS 2.2 Menthol/mCC/NNS).

In total, 62 eligible, healthy smoking subjects will be randomized into one of the 4 sequences:

Sequence 1: THS 2.2 Menthol → mCC (N=22).
Sequence 2: mCC → THS 2.2 Menthol (N=22).
Sequence 3: THS 2.2 Menthol → NNS (N=9).
Sequence 4: NNS → THS 2.2 Menthol (N=9).

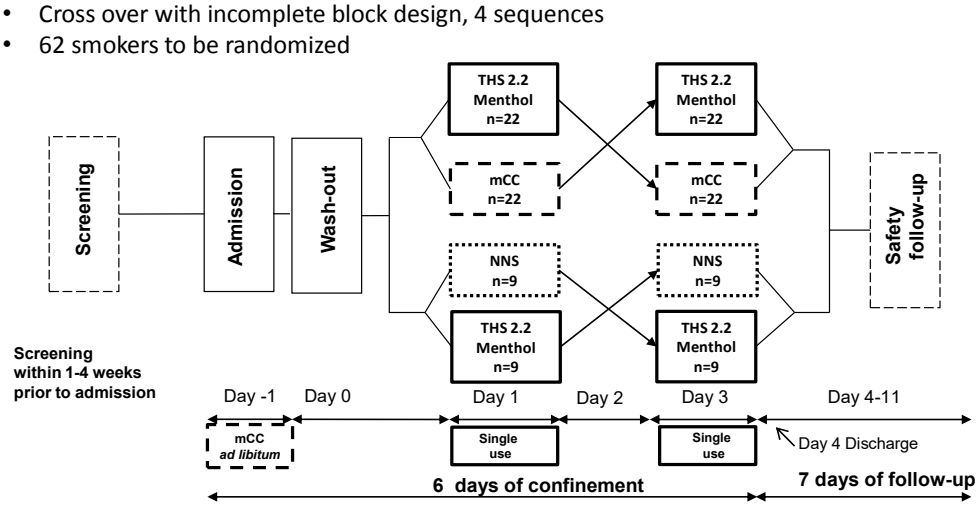
This procedure will lead to an incomplete block design with every subject being exposed to 2 of the 3 study products, as the comparison between NNS and mCC will not be considered:

mCC vs. THS 2.2 Menthol → (N=22 in both sequence 1 and 2).
THS 2.2 Menthol vs. NNS → (N=9 in both sequence 3 and 4).

Subjects will be randomized to sequence 1 and 2 (Group-1) and independently to sequence 3 and 4 (Group-2). Each sex and each of the smoking strata (International Organization for Standardization [ISO] nicotine levels ≤1 mg and >1 mg) will have a quota applied to ensure they represent at least 40% of the total study population for each of the Group-1 and Group-2.

Subjects will be discharged at time of discharge from the investigational site in the morning of Day 4 after all examinations of the Day of Discharge have been conducted. After the time of discharge, a 7-day safety follow-up will be started for the recording of spontaneously reported new AEs/SAEs and for active follow-up of ongoing AEs/SAEs. Any AE will in general be followed up until resolved, stabilized i.e., no worsening of the event, or until a plausible explanation for the event has been found.

Figure 1 Study Flowchart



THS: Tobacco Heating System; *mCC*: menthol conventional cigarette(s); *NNS*: nicotine nasal spray

The study will be conducted as a single-center study. For practical reasons, it will be conducted in several cohorts.

4.2 Rationale for Study Design and Control Groups(s)

The minimum age of 22 years age in the inclusion criteria was selected based on:

- The legal age of smoking in some US states is 19 years.
- To account for the 3 years of smoking history.

There are over 1,000 brands and sub-brands of CC that are sold in the United States. Most recent Federal Trade Commission (FTC) data show that menthol brands represented about 26% to 27% of market share of CC between 2003 and 2005. The leading mCC brands sold in the United States during that period were Newport, Marlboro Menthol, Kool, and Salem (FTC, 2009). Similar to

nonmenthol CC brands, the leading mCC brands have a variety of subbrands. Subbrands of the same brand vary in FTC-measured nicotine levels (Carabello et al, 2011). To reflect a representation of the market share of those brands in our study, a limited amount of sub-brands from each brand have been selected as reference products in our study, namely: Kool mild, Kool, Newport Menthol Short, Newport Menthol, Newport Menthol 100, Camel menthol silver, Camel menthol, Marlboro Menthol and sub-brands.

In this study, the selected mCCs described above will be used as a reference product and a market-approved pharmaceutical NNS (Nicotrol®NS 10 mg/mL) will be used as non-investigational reference point.

In the US, the NNS has been selected as the reference because it is the only nicotine replacement therapy (NRT) product that provides a rapid absorption of nicotine and is most similar in nicotine absorption rate compared to smoking (Benowitz et al., 2009). Nicotine from other NRT products has a much slower rate of absorption and the level in the blood from these products increases at a slower rate compared to smoking (Henningfield, 1995).

In the study, NNS will serve as a reference point in comparison with THS 2.2 Menthol for the following endpoints:

- Nicotine PK parameters.
- Urge-to-smoke.
- Safety.

The nicotine wash-out period was set to at least 24 hours (>5 x elimination $t_{1/2}$) as the elimination $t_{1/2}$ of nicotine in blood is around 2 hours in Caucasian smokers, the subjects who form the majority of the US population and therefore the majority of the expected study population (Benowitz et al., 2009, U.S. Census Bureau, 2010). There are no restrictions on race in the inclusion/exclusion criteria.

Cotinine will be also measured in addition to nicotine in this study to get information on the levels of cotinine levels in the study popuplation as it is described in the literature that the levels of cotinine are higher in black smokers as compared to white smokers (Carabello et al, 2011).

The use of estrogen contraceptive is known to accelerate nicotine clearance by 20%-30% in women as compared to women who do not take such contraceptives (Benowitz et al., 2006). Therefore, for the purpose of this study, it is not allowed to use hormonal contraception containing estrogens. This also applies to hormone replacement therapy.

In this study, THS 2.2 Menthol will be tested against mCC. The effect of menthol on nicotine metabolism has been suggested but remains inconclusive to our knowledge (Hukkanen et al., 2005). The activity of CYP2A6 will be measured at baseline as nicotine metabolism by CYP2A6 varies between individuals of the same ethnicity/race and across ethnicity/race due to genetic variations. These genetic differences could be associated with reduced/increased nicotine metabolism (Hukkanen et al., 2005).

4.3 Study Duration

The entire study per subject will last 14 to 41 days, including a Screening period of up to 28 days prior to Admission (Day -29 to Day -2), and 6 days of confinement (Day -1 to time of discharge on Day 4). In the morning of Day 4, the Day of Discharge examinations will be conducted. After the time of discharge, subjects will then enter a 7-day safety follow-up (until Day 11) for the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site.

4.4 Appropriateness of Measurement

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

All used questionnaires except cough and socio-economic status questionnaires are available as validated questionnaires.

5 STUDY POPULATION

5.1 Selection of Study Population

Sixty-two female or male smoking healthy adult subjects, who smoke at least 10 mCC per day will be randomized into this study. The maximum number of mCC is not limited. Subjects must have a smoking history of at least 3 years of consecutive smoking prior to Screening. Subjects can smoke different brands until Admission to the clinic. From Admission to the clinic onwards, however, they must restrict themselves to one preferred mCC brand.There will be a brand restriction for menthol flavored cigarettes: Kool mild, Kool, Newport Menthol Short, Newport Menthol, Newport Menthol 100, Camel menthol silver, Camel menthol, Marlboro Menthol and sub-brands.

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The smoking status of the subjects will be verified based on a urine cotinine test (cotinine ≥200 ng/mL). No restriction will be made with respect to races and ethnicities.

5.1.1 Inclusion Criteria

Inclusion Criteria	Rationale	Screening	Day of Admission (Day -1)
1. Subject has signed the ICF and is able to understand the information provided in the Subject Information Sheet and ICF.	Administrative	X	
2. Subject is aged from 22 to 65 years (inclusive).	Safety	X	
3. Smoking, healthy subject as judged by the Investigator based on all available assessments in the Screening period/day of Admission (e.g., safety laboratory, spirometry [forced expiratory volume in 1 second {FEV_1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV_1 >80% predicted value, and	Safety	X	X

Inclusion Criteria	Rationale	Screening	Day of Admission (Day -1)
post-bronchodilator FVC >0.8], vital signs, physical examination, ECG, chest X-ray, and medical history).			
4. Subject smokes at least 10 commercially available menthol CCs per day for the last 4 weeks, based on self-reporting (with brand restrictions). Furthermore, the subject has been smoking for at least the last 3 consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine ≥200 ng/mL).	Effect	X	X
5. The subject does not plan to quit smoking in the next 3 months.	Safety	X	
6. The subject is ready to accept interruptions of smoking for up to 4 days.	Safety	X	X
7. The subject is ready to accept using both the THS 2.2 Menthol and NNS products.	Effect		X

5.1.2 Exclusion Criteria

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

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -1)
1. As per Investigator judgment, the subject cannot participate in the	Safety	X	X

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -1)
study for any reason (e.g., medical, psychiatric, and/or social reason).			
2. A subject who is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, subject in a social or sanitary establishment, prisoners, or subjects who are involuntarily incarcerated).	Administrative	X	
3. The subject has medical condition requiring smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Investigator.	Safety	X	X
4. The subject has a body mass index (BMI) <18.5 or ≥35.0 kg/m^2.	Safety	X	
5. As per Investigator judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.	Effect	X	X

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -1)
6. The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT), as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.	Effect	X	X
7. The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug prior to the Admission Day (Day -1; whichever is longer) which has an impact on CYP2A6 activity.	Effect		X
8. In case the subject received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -1), it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives and subject's safety.	Effect	X	X
9. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with subject's participation in study.	Administrative	X	X
10. The subject has a positive urine drug test.	Administrative	X	X
11. Positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.	Safety	X	
12. Donation or receipt of whole blood	Safety	X	X

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -1)
or blood products within 3 months prior to Admission.			
13. The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).	Administrative	X	
14. The subject is an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, child).	Administrative	X	
15. The subject has participated in a clinical study within 3 months prior to the Screening Visit.	Safety	X	
16. The subject has previously participated in the same study at a different time (i.e., each subject can be included in the study population only once).	Administrative	X	
17. For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding.	Safety	X	X
18. For women only: Subject does not agree to use an acceptable method of effective contraception.*	Safety	X	X

* Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, 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. Hormonal contraception with estrogen containing products is NOT allowed in this study.

5.1.3 Removal of Subjects from the Study

Subjects will be informed that they are free to withdraw from the study at any time. Subjects should be questioned for the reason of premature withdrawal, although they are not obliged to disclose it. This needs to be fully documented in source documents and reported in the electronic Case Report Form (eCRF).

When a subject withdraws or is removed from the study, the whole examination procedure planned at the Day of Discharge (Day 4) must be performed as soon as possible after the time of withdrawal unless subject withdrew the informed consent to do so. After the time of withdrawal, the subject will enter into the 7-day period of safety follow-up. Subjects withdrawn or removed from the study cannot re-enter the study.

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

- Withdrawal of informed consent.
- Any AE or condition (including clinically relevant changes in a laboratory parameter) which at the discretion of the Investigator.
- Positive pregnancy testing (no invasive procedures including the drawing of blood must be performed after detection of pregnancy, see Section 8.5)
- Female subjects starting estrogen containing contraception or hormone replacement therapy containing estrogens during the study.
- The use of any nicotine/tobacco product which is different from the assigned product.
- The Sponsor or Investigator terminates the study.
- Withdrawal is considered to be in the best interest of the subject or the other subjects.

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

- Lost to follow-up.

- Concomitant treatment with non-authorized medication as defined in the context of this study (in general, any concomitant medication should be discussed with the Contract Research Organization [CRO] Medical Monitor on an ongoing basis).

- Non-compliance to the study procedures.

Subjects withdrawn prematurely after randomization will not be replaced and will not be allowed to re-enter. All withdrawals have to be documented properly in the eCRF.

5.1.4 Violation of Selection Criteria

Subjects who are eligible at Screening but who do not meet the entry criteria at Admission (Day -1) prior to enrolment will be considered a screening failure and will be replaced by other subjects.

Subjects who violate the entry criteria after enrolment, but who are considered eligible, will be immediately withdrawn from the study when the violation is detected. Such subjects will not be replaced.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

THS 2.2 Menthol

The THS 2.2 Menthol will be provided by the Sponsor and its distribution will be limited to a qualified and appropriately trained investigator or designee.

THS 2.2 Menthol comprises the following components: Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable (see the user guide in Appendix 3):

Charger:	The function of the Charger (Model 4) is to recharge the Holder after use. It contains a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around, and can itself be recharged from a mains power source.
Tobacco Stick Holder (Holder):	The function of the Holder (Model 4.2) is to heat the Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Tobacco Stick)
THS Menthol Tobacco Stick (Menthol Tobacco Sticks):	The Menthol Tobacco Stick (product code C3) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder.

The overall objective of the design is to provide an acceptable experience in which the HPHC level in the aerosol is substantially reduced in comparison with CCs.

Per cigarette/Tobacco Stick tar, nicotine, and carbon monoxide yields are normally determined by standardized test methods. The most widely used test method is ISO 4387. PMI has developed a modified version of this method, which improves the determination of tar in products with high water content, which is typical for heated tobacco products (PMI, 2012b, PMI, 2012c, PMI, 2013b). Another method is the more intensive smoking method developed by Health Canada (Health Canada, 1999).

Table 1 below lists the commonly reported measures (PMI, 2013a).

Table 1 Measured Aerosol Fractions for the THS Menthol Tobacco Sticks

Constituent (mg/THS Tobacco Stick)	ISO [1]	Health Canada Intense regime [2]
Tar/NFDPM	5	12.6
Nicotine	0.5	1.2
Carbon monoxide	1	0.6

[1] International Organization for Standardization ISO machine-smoking regimen. The analytical method has been modified to avoid inaccuracies as a result of condensation from high water-content aerosols.

[2] Health Canada Intense machine-smoking regimen (55 mL puff volume, 2-second puff duration, 30-second inter-puff interval) (Health Canada, 1999)

Menthol CC

In the study sequences 1 and 2, the reference product to THS 2.2 Menthol is commercially available single brand mCC.

Menthol CC will not be provided by the Sponsor. All eligible subjects will be asked to purchase their own preferred single-brand mCC prior to Admission. As randomization takes place on Day 0, every study subject needs to buy his/her anticipated amount of single-brand mCC for a total of 2 days plus 2 extra packs.

6.2 Reference Point Product

The NNS Nicotrol®NS (10 mg/mL) will be the reference point product to THS 2.2 Menthol for sequences 3 and 4. The NNS will be supplied by the Investigator and reimbursed by the Sponsor. One spray will be administered into each nostril per product use, leading to a total administered dose of 1 mg nicotine/product use as per label.

6.2.1 Packaging and Labeling

At Admission on Day -1, all study subjects will provide the anticipated amount of mCC in sealed packs to the site staff. The cigarette packs provided by the subject should not be opened and the cellophane should be intact.

Each pack of cigarettes provided by the subject will be labeled to identify which subject the cigarettes belong to (labels should be affixed to the cellophane of the lower part of the pack).

Packs of mCC will be labeled to identify necessary information to match the subject with his/hers suppliers.

For the Menthol Tobacco Sticks, the packs will be printed with the necessary information including, but not limited to, health warning, tar, nicotine, and CO ISO levels, product code, and expiry date.

6.3 Use of Investigational and Reference Point Products

Subjects will never be requested or forced to smoke and will be free to stop smoking at any time of the study. Subjects caught using any nicotine/tobacco product which is different from the assigned product will be withdrawn from the study. During the screening period, subjects will be allowed to smoke according to their smoking habits except during the procedures of the screening visit (see section 9.1).

6.3.1 Admission (Day -1)

Subject will be instructed not to smoke in the morning prior to Admission. Smoking *ad libitum* will be allowed throughout the day of admission except during the procedures until 11:00 PM. All subjects will be allowed to continue smoking *ad libitum* their own mCC. All subjects (except women with a positive pregnancy test at Screening or Admission) will undergo a THS 2.2 Menthol test first and subsequently a NNS test at Day -1 prior to enrolment.

Following agreement that the THS 2.2 Menthol is acceptable, subjects will be randomized to one of 4 product exposure sequences using an Interactive Web Response System.

6.3.2 Investigational Period (Day 0 to Day 3)

During the first washout, each subject will maintain nicotine abstinence from Day -1 at 11:00 Pm to the time of single use of his/her allocated product at Day 1. At Day 1, after the single use of the product, subjects will maintain nicotine abstinence for the rest of the day. During the second washout on Day 2, subjects will maintain nicotine abstinence until the time of single use of his allocated product at Day 3. Subjects will not be allowed to smoke or use any other nicotine/tobacco-containing products other than the products they are allocated to.

Time point 0 will be defined as start of the single product use on the single use days or as start of the first product use on each study day. The start of product use for THS 2.2 Menthol is defined as the time of the first puff. The start time for mCC corresponds to the lighting of the mCC, and the start time of the product is the time of the spray in the first nostril. The 30 seconds it takes to pre-heat the tobacco stick holder will not be taken into account. **The subject must not take a puff of the tobacco stick during the pre-heating time**.

The start of the first product use can be different for each subject both days of product use. However, it must be in the window of 6:00 AM to 9:00 AM.

Single use of products (Day 1 and Day 3)

On Day 1 and Day 3, subjects will use the product they are randomized to only once in the morning between 6:00 AM to 9:00 AM, and will abstain from the product or other nicotine/tobacco-containing items for the rest of the day, i.e., subjects in the THS 2.2 Menthol arm will use one Menthol Tobacco Stick, subjects in the mCC arm will smoke one mCC, and subjects in the NNS arm will spray once into each nostril (leading to an estimated total administered amount of 1 mg nicotine), as shown:

	Sequence 1	Sequence 2	Sequence 3	Sequence 4
Day 1	THS 2.2 Menthol	mCC	THS 2.2 Menthol	NNS
Day 3	mCC	THS 2.2 Menthol	NNS	THS 2.2 Menthol

6.3.3 Day of Discharge/Time of Discharge

On the Day of Discharge (Day 4), smoking will be only allowed after all laboratory procedures and the spirometry have been performed. All examinations of the Day of Discharge will be conducted on Day 4 prior to the time of discharge.

6.3.4 Safety Period

During the safety follow-up period, subjects are free to smoke according to their usual smoking habits.

6.3.5 Stopping Rules for Investigational Product

For safety purposes, using the THS 2.2 Menthol or smoking the mCC or the use of the NNS 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 Investigator.

6.4 Method for Assigning Subjects to Study Arms

Randomization to product exposure sequence will be done through an Interactive Telephone and Web Response System.

Each sex and each of the smoking level (ISO nicotine levels ≤1 mg and >1 mg) will have a quota applied to ensure they represent at least 40% of the total study population allocated within each of the two groups:

- Group-1: composed of sequences 1 and 2.
- Group-2: composed of sequences 3 and 4.

In particular, the maximum number of subjects having the same sex or nicotine level value will be limited to 26 in Group-1 and 10 in Group-2.

The randomization of the planned sample size of 62 subjects will be ensured by applying quota to the number of subjects per each sequence (22 subjects for sequences in Group-1, and 9 subjects for sequences in Group-2).

Subjects will be randomly assigned to one of the four product exposure sequences by means of a permuted-block schema. Block size and other randomization details will be available in the randomization plan.

The randomization plan will be generated by an independent statistician and none of the sponsor staff, investigators, and study subjects will have access to the randomization schema prior to randomization.

6.5 Blinding

This is an open-label study; therefore the subjects and investigators or designee will be unblinded to subject's sequence. However, there will be a limited degree of blinding in the data review and data analysis process. In particular, PMI and CRO personnel will be blinded to the randomized sequence as summarized in the following table:

Blinded Study Personnel	End of Blinding Period
PMI and CRO study statisticians	After the SAP finalization or PMI blind database review(*), whichever comes last.
PMI data manager	After the finalization of PMI blind database review.(*)
PMI safety and clinical scientist	After the finalization of PMI blind database review(*). Can be actively un-blinded before that time point in case of the occurrence of any safety question, when appropriate.

(*) As part of the PMI Quality Control activity, data listings will be reviewed by PMI before database lock, with no access to the randomization sequence information.

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

6.6 Investigational Product Accountability and Compliance

6.6.1 Dispensing Investigational Product

From Day -1 until Day 4, the THS 2.2 Menthol, NNS, and mCC will be dispensed by the Investigators or dedicated study staff, as per study design. Each dispense of the product will be recorded. In addition, the start times of using any product must be recorded for Day 1 and Day 3. The product will not be promoted for commercial distribution or test market.

6.6.2 Storage and Accountability

The THS 2.2 Menthol, NNS, and mCC will be stored in a secured site storage place with access limited to the authorized personnel only. Full accountability of the distributed products will be ensured by designated staff. Subjects will return each butt of any used Menthol Tobacco Stick or mCC immediately after use to the site staff for accountability. They will also return the NNS after use to the site staff. The time of return of the products will be documented in appropriate log. At the end of the study, unused mCCs given to the site staff at Admission on Day -1 will be given back to the subjects.

6.6.3 Investigational Product Retention

Unused Menthol Tobacco Sticks and NNS will be destroyed or returned to the Sponsor upon study completion. The Tobacco Heating Devices will be returned to the Sponsor as well.

6.6.4 Compliance to Investigational Products

Compliance for all arms will be ensured by strict distribution of the products (product by product) and collection of used Tobacco Sticks, the CC butts and the NNS after use will be documented in appropriate logs.

In addition, in subjects using NNS, the compliance will be chemically verified using exhaled CO breath. The cut-off point for the CO breath test value to distinguish tobacco use vs. no tobacco use will be 10 ppm (Beal, 1989).

Furthermore, the CO breath test will be considered as one of the measures of compliance during the wash-out days in all subjects.

6.7 Restrictions

6.7.1 Smoking Restrictions

On Day 1 and Day 3, to avoid nicotine cross contamination, smokers of THS 2.2 Menthol and mCC will smoke in dedicated separate rooms: one room for THS 2.2 Menthol and one room for mCC. Every subject must smoke alone with an interval between subjects allowing ventilation of the room. Subjects receiving NNS must not have access to these rooms.

In the morning prior admission, subjects will be instructed not to smoke. At admission, smoking is only allowed during the designated smoking times from 6:00 AM to 11:00 PM as detailed in the study design. Subjects will not have free access to their NNS, mCC or, Menthol Tobacco Sticks which will be dispensed by the site staff individually as described in Section 6.6.1.

Smoking is not allowed during study procedures except during blood sampling for nicotine PK on Day 1 and Day 3. Furthermore, smoking is not allowed on Day 4 until all laboratory tests and the spirometry have been conducted.

During the days of wash-out or single product use (for CC and THS 2.2 arms), no NNS or other products supportive to smoking abstinence must be used or will be provided to the subjects.

6.7.2 Dietary Restrictions

A standard diet will be designed by a dietician for the whole confinement period. For each meal, the caloric and fat content should be controlled in order to avoid a “high-fat” diet. The FDA guidance on food-effect studies for bioequivalency 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) (FDA, 2002).”

Subjects are not allowed to bring their own food or beverages to the investigational site. Meals will be served according to the schedules provided in Section 9. Additional light snacks, fruits, and raw vegetables can be distributed to the subjects without restrictions at any time during confinement as long as they comply with the dietician’s standard diet. Consumption of water is allowed as desired. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed. The same menu and meal schedule will be administered uniformly for all subjects in all study arms. Fasting state has to be observed for at least 10 hours prior to blood drawings for the safety laboratory on the Screening Visit, on Day -1 and Day 4.

6.7.3 Concomitant Medication

For the purpose of this study, no concomitant medication should be taken from screening to the EOS (time of discharge plus 7 day safety period) by the subjects without prior informing the Investigator or designee. Any medication with an impact on the CYP2A6 metabolism (as prescription and over-the-counter products) as given below must be avoided as CYP2A6 is involved in the nicotine metabolism.

In this study, it is NOT allowed to use hormonal contraception containing estrogens. This also applies to hormone replacement therapy. Hormonal contraception with products containing progesterone only is allowed during this study. Subjects using estrogens during the study will be withdrawn.

The following drugs and substances are considered having an impact on CYP2A6 activity (Lacy et al., 2007: Table 2). Prior to database close, the concomitant medication will be assessed according to the potential impact on CYP2A6 activity and the potential impact on study results.

Table 2 Drugs and Substances Considered Interacting with CYP2A6

Drug name	Substance Class
Fluoroquinolones, including ciprofloxacin and ofloxacin, nafcillin, rifampicin	Antibiotic
Fluvoxamine, fluoxetine, paroxetine, bupropion, duloxetine, amitriptyline, imipramine, sertraline, mirtazapine, citalopram, thioridazine	Antidepressant
Haloperidol, perphenazine, chlorpromazine, propoxyphene fluphenazine, clozapine, olanzapine	Neuroleptic
Phenobarbital, primidone, carbamazepine	Antiepileptic
Cholorquine, quinidine	Antirheumatic
Clotrimazole, terbinafine, fluconazole, ketoconazole, miconazole	Antimycotic
Erythromycin, ciprofloxacin, clarithromycin, norfloxacin	Antibiotic
Cimetidine, chlorpheniramine, diphenhydramine, ranitidine	H2-receptor antagonist
Amiodarone, verapamil, mibefradil, mexiletin, propafenone, propanolol, lidocaine	Antiarrhythmic
Losartan, amlodipine, nifedipine, losartan	Antihypertensive

Drug name	Substance Class
Drosperinone, estrogens	Hormonal contraceptives, Agents for hormonal replacement therapy (estrogens)
Fluvastatin	Cholesterol-lowering agent
Theophylline	Antispasmodic pulmonological agent/Bronchodilator agent
Omeprazole, Lansoprazole	Proton pump inhibitor
Interferon	Antiviral/Immunomodulating agent
Methoxsalen	Anti-psoriatic (substance class Furocoumarins)
Modafinil, Diclofenac, Rofecoxib	Analgesic
Insulin	Anti-diabetic
Sildenafil	Phosphodiesterase-Inhibitor (e.g., used for treatment of Erectile dysfunction)
Quinine	Crystalline alkaloid
St. John's Wort	Over-the-counter (herbal remedy) antidepressant
Psoralen	Anti-psoriatic (substance class Furocoumarins)
Pilocapine	Cholinergic agonists (e.g., used for Glaucoma Therapy)

Data sources: Lacy et al., 2007. This list is not exhaustive

However, the Investigator is responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescription of medication will be taken in the best interest of the subject.

If the use of a concomitant medication cannot be avoided for the subject's safety, it has to be fully documented (for details, see Section 7.4.5). Concomitant medications should be followed up with the CRO Medical Monitor on an ongoing basis.

Concomitant medication will first be assessed at Screening Visit. To be eligible for the study, any medication with impact on CYP2A6 metabolism must be discontinued at least 14 days prior to Admission to the clinic or for at least five half-lives (whichever is longer). They must not be used during the entire study until the time of discharge. It is at the discretion of the

Investigator to assess if a termination of such medication at Screening is medically justified and safe for the subject.

6.7.4 Other

From admission to discharge, practice of intensive exercise and physical work-out will be prohibited as it may impact the nicotine absorption profile.

7 STUDY PROCEDURES

Personnel performing study measurements or recording must have the appropriate training fully documented. Quality and control measures have to be in place. All study procedures are provided as an overview in the Schedule of Events (Appendix 1). In this Section, only the expected/planned time points for the various measurements are given. Considering that not all subjects can have a procedure at the same time point, adequate time windows will be given for each study procedure and each time point in Section 9. Site personnel will adhere to the site's Standard Operating Procedures (SOPs) for all activities relevant to the quality of the study. Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

7.1 Informed Consent Form/Subject Information Sheet

Each subject must give his/her informed consent prior to participating in the study. During the consent process, the Investigator obtaining consent must inform each subject of the nature, risks and benefits of, and alternatives to study participation. In addition, each subject must review the Subject Information Sheet and ICF/subject information sheet and must have sufficient time to understand and have adequate opportunity to ask questions. The ICF/subject information sheet must be signed and dated prior to undertaking any study-specific procedures. A signed copy of the ICF/subject information sheet should be given to the subject.

7.2 Smoking Cessation Advice and Debriefing

Each subject will be given advice on the risks of smoking, with smoking cessation advice, three times during the study: at the Screening Visit, at Admission (Day -1), and at Day of Discharge (Day 4). This will take the form of a brief interview according to current US recommendations (U.S. Public Health Service, 2008). Details of the interview will be recorded in the Source Document File. Information on the risk of smoking will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the Investigator or designee and may additionally be given in a group session.

In addition to the smoking cessation advice, a debriefing of subjects will be done at each smoking cessation advice session to address any intended or unintended beliefs participants have about the candidate MRTP. The goal of the debriefing would be to help ensure that subjects exit the study with an accurate understanding of product risks, including an understanding that the candidate MRTP has not been demonstrated to be less harmful than CC.

7.3 Support during Smoking Abstinence/Periods of Reduced Smoking

All subjects will be closely monitored by the site staff. This includes monitoring of clinical tests e.g., vital signs, physical examination, and body weight. It also refers to close monitoring of the subject's behavior, AEs, and his/her mood.

7.4 Clinical Assessments

Any clinically relevant finding detected during the Screening Visit has to be documented as a concomitant disease. This also applies to clinically relevant findings in laboratory values, vital signs, and ECGs, detected during the Screening Visit. Any untoward medical occurrence in a subject detected during the study which was not present at the Screening Visit must be documented as an AE. Worsening of a pre-existing condition from the Screening Visit onwards will also be documented as an AE. If a clinically relevant finding is detected during the Screening period, the Investigator needs to check if inclusion criterion number 3 is still fulfilled.

7.4.1 Demographic Data

Demographic data (sex, date of birth/age, and race) will be recorded at the Screening Visit.

7.4.2 Identification of the Current Cigarette Brand

Identification of the current mCC brand smoked by the subject will be done at the Screening Visit and at Day -1. For the Screening Visit, subjects will be asked to bring a packet of their current mCC brand to the site. At Day -1, subjects have to hand their mCC supply for the confinement period to the site staff, who will take a photograph of the front and of the side of a cigarette pack supplied by the subject and will document brand name and yields. Photos will be considered as Source Documentation. A copy of the photos will be provided to the Sponsor electronically as DVD or CD.

7.4.3 Smoking History and Willingness to Quit Smoking

Subjects will be questioned for their smoking history. At Screening and day of Admission, this will include questions to evaluate whether the subject was a smoker for at least the last three consecutive years, to determine the number of mCC smoked during the previous 4 weeks, and to evaluate if the CCs smoked during the previous 4 weeks were menthol. Yields will later be ascertained, based on the cigarette brands. At the Screening Visit only, the subject will also be asked if he/she is planning to quit smoking during the next 3 months. In addition, the subject will be asked if he/she has used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT), electronic cigarettes, or similar devices, within 4 weeks prior to assessment.

Furthermore, subjects will be asked if they are ready to abstain from smoking/accept reduced smoking frequency for up to 4 days. Only subjects prepared and able to comply with this requirement will be considered for participation in the study.

7.4.4 Demonstration and Product Tests of THS 2.2 Menthol and NNS

All subjects will have a demonstration of the THS 2.2 Menthol and the NNS products at the Screening Visit. On Day -1 as the last procedure of the eligibility assessments on that day, subjects will have a product test prior to enrolment, THS 2.2 Menthol (using up to three Menthol Tobacco Sticks) first and subsequently NNS (spraying once in each nostril). In female subjects, the THS 2.2 Menthol and NNS product tests must only be done after pregnancy is excluded by a negative urine pregnancy test. Only subjects willing and ready to use the THS 2.2 Menthol and the NNS and be randomized to any of the study arms can be enrolled into the study.

7.4.5 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical history and any concomitant disease will be documented at the Screening Visit. Medical history is defined as any condition that started prior to and ended prior to Screening. A concomitant disease is defined as any condition that started prior to the Screening Visit and is still ongoing at the Screening Visit.

Priormedication taken within 4 weeks prior to Screening and any concomitant medication needs to be documented. Any medication which was started prior to the Screening Visit and is still being taken by the subject will be considered a concomitant medication. Medication initiated after Screening is also referred to as concomitant medication. This applies to both prescription and over-the-counter products.

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

7.4.6 Physical Examination

A physical examination will be conducted at the Screening Visit, at Admission (Day -1), and at the Day of Discharge (Day 4).

7.4.7 Body Height and Weight

Body weight will be recorded at the Screening Visit, at Admission (Day -1) and at the Day of Discharge (Day 4). Body height will be measured at the Screening Visit only. The BMI will be calculated from the body weight and height using the following formula, rounded to the first decimal place:

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

7.4.8 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured at the Screening Visit, at Admission, and at every day in confinement. All parameters will be recorded in supine position after the subject has rested for at least 5 minutes.

For every measurement, it has to be documented if the subject has smoked within 15 minutes prior to the measurement.

7.4.9 Other Clinical Assessments

7.4.9.1 Spirometry

Spirometry with and without a short-acting bronchodilator will be done at the Screening Visit to evaluate inclusion/exclusion criteria (the post-bronchodilator results). At screening, spirometry without bronchodilator will be done first, and then, spirometry with bronchodilator. Spirometry with bronchodilator at screening be used for eligibility Furthermore, spirometry without a bronchodilator will be performed on Day-1 as well as on Day 4.

Spirometry will follow the 2005 testing and quality recommendations by the American Thoracic Society/European Respiratory Society Joint Task Force on the standardization of spirometry along with the electronic data submission and documentation processes (American Thoracic Society (ATS), 2005). Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set (Hu and Cassano (NHANES III), 2000).

All personnel performing lung function testing should have the appropriate training and quality control measures should be put into place and be properly documented and filed at

the pulmonary function laboratory (including the records of the calibration, if applicable). The FEV_1 and FVC will be recorded.

The subject will be submitted to a spirometry with maximum voluntary ventilation MVV measurement.

For spirometry, assessed parameters will include:

- $FEV_{1.}$
- FVC.
- FEV_1/FVC.

7.4.9.2 Electrocardiogram

An ECG will be recorded at Screening and on the following study days: Day 1 and Day 3. The ECG testing will be performed as per the site local practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval, corrected by the ECG device according to Bazett's formula. Every ECG has to be assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis has to be provided in the eCRF for all ECGs assessed as abnormal – clinically relevant. ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied, initialed, dated, and stapled together for inclusion in the Source Data File.

7.4.9.3 Chest X-ray

A chest X-ray (anterior-posterior and left lateral views) will be assessed during the Screening period to exclude subjects with relevant pulmonary diseases. Subjects will be referred to a radiology facility for this procedure. No new examination is required if the subject can present a chest X-ray with anterior-posterior and left lateral views at the Screening Visit which is not older than 6 months.

7.5 Biomarker Assessment

All bioanalytical assays and laboratory assessments (Section 7.6) will be carried out using validated methods. The bioanalytical methods used will be documented in the Bioanalytical Reports. A list of laboratories is provided in Appendix 2.

The start time of the use of each product has to be documented on single use days (Day 1 and Day 3).

Precautions should be taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine or CO.

7.5.1 Biomarker of Exposure

7.5.1.1 Biomarkers of Exposure to CO and COHb

COHb measured in blood and exhaled CO will be investigated as a measure of exposure to CO. The CO breath test will also serve as a measure of compliance in subjects using NNS as well as on the wash-out days in all subjects.

CO Breath Test

CO in exhaled breath will be measured using the Smokerlyzer® device such as Micro+™ Smokerlyzer® device or similar. The test will performed in all subjects including the subjects using the NNS.

A CO breath test will be conducted once on Day -1 and Day 4:

On Day 0, Day 1, Day 2, and Day 3, four CO breath tests will be done per day. On Day 1 and Day 3, the first test per day will be performed within 15 minutes prior to T_0. The three other tests will be conducted as described in section 9. On the wash-out days (Day 0 and Day 2), four tests will be conducted as described in section 9.

Carboxyhemoglobin

Tests for COHb measurement will be performed at a local laboratory.

Blood samples will be taken as follows at Day 1 and Day 3:

A total of five blood samples will be taken. The first sample will be taken within 15 minutes prior to using the first product (T_0). Thereafter the sampling times in relation to T_0 are at 15 minutes, 60 minutes, 4 hours, and 12 hours post-T_0.

7.5.1.2 Biomarkers of Exposure to Nicotine

Blood samples to measure nicotine in plasma will be taken as follows:

Single Use Day 1 and Day 3:

A total of 16 blood samples will be taken for a 24-hour profile. The first blood sample will be taken within 15 minutes prior to the single use (Day 1 and Day 3, T_0). Times of sampling are

thereafter in relation to T_0: T_1 after 2 minutes, T_2 after 4 minutes, T_3 after 6 minutes, T_4 after 8 minutes, T_5 after 10 minutes, T_6 after 15 minutes, T_7 after 30 minutes, T_8 after 45 minutes, T_9 after 60 minutes, T_{10} after 2 hours, T_{11} after 4 hours, T_{12} after 6 hours, T_{13} after 9 hours, T_{14} after 12 hours, and T_{15} after 24 hours (this sample will be drawn during the day following product use, i.e., wash-out).

In these 16 blood samples, cotinine will be measured together with nicotine at all corresponding timepoints. However, only the data from the three following time points: prior T_0, $T_{0 + 12 \text{ hours}}$ (T_{14}), $T_{0 + 24 \text{ hours}}$ (T_{15}) will be used for analysis. This is to avoid additional blood sampling for the subject as nicotine and cotinine are measured in the same assay.

7.5.2 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Day -1 (Jacob et al., 2011). CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites. In this study the CYP2A6 activity will be measured using the metabolic molar ratio of *trans*-3'-hydroxycotinine/cotinine.

7.6 Laboratory Assessments

A list of laboratories is provided in Appendix 2.

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

Hematology, clinical chemistry, and urine analysis for the safety panel will be measured at Screening, at day of Admission (Day -1), and at the Day of Discharge (Day 4). Tests will be conducted at a local laboratory or the site. Blood will be taken after no less than the 10 hours of fasting (see Section 6.7.2). The urine test will be performed semi-quantitatively as urine dip-stick test at the site. Parameters to be measured are listed in Table 3.

Table 3. 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 (WBC) count - Differential WBC count: • Neutrophils • Basophils • Eosinophils • Lymphocytes • Monocytes	- Albumin - Total protein - Alkaline phosphatase - Alanine aminotransferase - Aspartate aminotransferase - Blood urea nitrogen - Creatinine - Gamma-glutamyl transferase - Fasting glucose - Lactate dehydrogenase - Potassium - Sodium - Total bilirubin - Direct bilirubin - Total cholesterol - Triglycerides	- pH - Bilirubin - Glucose - Nitrite - Red blood cell traces - Protein - Specific gravity

7.6.2 Serology

A test for Hepatitis B surface antigen, Hepatitis C virus, and HIV (anti-HIV1/2 and p24 antigen) will be done at Screening. In case of positive results, the subject will be referred to appropriate medical care.

7.6.3 Urine Drug Screen

A urine drug screen will be performed at the site at the Screening Visit and at the day of Admission. The urine will be screened for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

7.6.4 Urine Cotinine Screening

A urine dip-stick cotinine test will be performed at Screening and at Admission to the clinic in order to confirm the subject's smoking status. The test must detect cotinine with a cotinine of ≥200 ng/mL, (i.e., One-Step Cotinine Test 008A086, Ultimed, Belgium).

7.6.5 Alcohol Breath Test

Subjects will undertake a breath alcohol test at the Screening Visit and at Admission to the clinic using an alcometer device.

7.6.6 Urine Pregnancy Testing

All female subjects will have pregnancy testing at the Screening Visit, at Admission to the clinic, and at the Day of Discharge (Day 4). Female subjects with a positive pregnancy test at the Screening Visit or on Day -1 cannot be enrolled and are considered a screening failure. Pregnancy in such subjects will not be followed up as no exposure to the THS 2.2 Menthol will have occurred. Product test at Admission must be done only in female subjects with a negative pregnancy test. In any case of a positive pregnancy test, the Investigator will inform the subject about the risks associated with smoking during pregnancy. In the event of unclear urine pregnancy test in peri-menopausal women, absence of pregnancy should be confirmed by a serum follicle stimulating hormone level >20 IU/l.

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

7.7 Sample Handling, Storage, and Shipment

Participating laboratories for blood samples testing will be decided prior to the Investigator Meeting and site initiation. Safety laboratory samples will be tested at a local laboratory (see (see Appendix 2). The urine dipstick for the safety laboratory, urine drug screen, urine pregnancy tests, and urine cotinine tests will be done by the site personnel at the site. The tests will be provided by the sites.

Detailed procedures for handling of samples are described in the separate Sample Handling Manual (SHM). Safety laboratory samples will be destroyed as by the laboratories standard procedures. All other samples will be destroyed once the CSR has been finalized. 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.

7.7.1 Blood samples

Blood samples will be drawn by qualified and trained site personnel. Subjects should be in a seated position during blood collection. In total, around 190 mL will be drawn for this study including planned assessments, safety, and repeated analysis for safety. This is less than a standard blood draw. The required aliquots and volumes for assessments of blood/plasma parameters and tests are summarized in the SHM.

7.7.2 Urine samples

Spot urine samples will be taken for urine drug screen, cotinine screen, pregnancy tests, and safety urinalysis.

7.8 Questionnaires

The subject questionnaires and the VAS will be entered by the subject directly in the electronic patient reported outcomes device or in paper copy. The questionnaires and the VAS will be reviewed for completeness by the study site staff and subjects will be requested to complete any missing information.

Symptoms or worsening of symptoms as documented on any of the questionnaires or the VAS do not need to be documented as AEs because the questionnaire and the VAS will be analyzed as part of the report. However, it is at the discretion of the Investigator to document such symptoms also as AEs. The main source for AE collection will be the face-to-face interview between the subject and site staff using, open, non-directive questions (see Section 8.2.1).

7.8.1 Fagerström Test for Nicotine Dependence (revised version)

Potential nicotine dependence will be assessed at Screening using the FTND in its revised version (Heatherton et al., 1991), as updated in 2012 (Fagerström et al., 2012).

The questionnaire consists of six questions which have to be answered by the subject himself/herself. The scores obtained on the test permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) (Fagerström et al., 2012).

7.8.2 Assessment of Cough

Subjects will be asked if they have experienced a regular need to cough, e.g., coughing several times in the last 24 hours prior to assessment. If the answer is ‘yes’, they will be

asked to complete a VAS, three Likert scales, and an open question also assessing the previous 24 hours.

The VAS will assess how bothersome cough is to the subject ranging from 'not bothering me at all' to 'extremely bothersome.'

Furthermore, subjects will be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales:

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

Finally, subjects will be asked with an open question if there are any other important observations that they would like to share with the staff about their coughing.

Assessments will be done on a daily basis from Day 0 to Day 4. On Day 2 and Day 4, questionnaire must be asked 24 hours after T_0 of Day 1 and after 24 hours after T_0 of Day 3.

7.8.3 Modified Cigarette Evaluation Questionnaire (modified version)

Product evaluation will be assessed using the MCEQ (Cappelleri et al., 2007). The MCEQ assesses the degree to which subjects experience the reinforcing effects of smoking, by measuring:

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

This questionnaire will only be completed by the subjects, who use the THS 2.2 Menthol or smoke mCCs during the study. The MCEQ will be completed by subjects on Day 1 and Day 3.

7.8.4 Questionnaire of Smoking Urges

To assess the urge-to-smoke, all subjects will be asked to complete a 10-item brief version of the QSU (Cox et al., 2001). The QSU-brief is a self-reported questionnaire with 10 items to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicate a higher urge-to-smoke.

The findings in this brief version were consistent with the expressions of craving found in the 32-item version of the QSU (Tiffany et al., 1991). The findings supported a multi-dimensional conceptualization of craving to smoke and demonstrated the utility of a brief multi-dimensional measure of craving (Cox et al., 2001).

The QSU-brief will be completed by the subject himself/herself at single use study days in all subjects.

The first assessment will be done within 15 min prior to T_0, 9 assessments thereafter in relation to T_0: 15 min, 30 min, 45 min, 60 min, 2 hr, 4 hrs, 6 hrs, 9 hrs, and 12 hrs after T_0 with a time window of 10 minutes each.

7.8.5 Socio-Economic Status Questionnaire

As part of the characterization of the study population it is important to measure variables that have been shown to be related to nicotine dependence and product reinforcing value. Based on prior tobacco research these factors include age, gender, ethnicity, tobacco use history, educational as well as socio-economic status.

Socio-economic status (SES) information is recorded in similar manner in the clinical program, in behavioral research and will be eventually assessed in postmarked studies once the product is commercialized. In order to predict and evaluate the effect of alternative, potentially less harmful tobacco product use might have in adult smokers the socio-economic status constitutes an important demographic characteristic. SES data will be reported cross the randomized clinical studies and will be collected in observational pre-market and post-market studies. This questionnaire will allow the Sponsor to assign the subject household's SES

At screening the subjects will be informed in detail about the exams and evaluations planned during the study, and similarly notified about the SES assessment which will be done on Day 2 once they provided informed consent and were enrolled into the study.

On Day 2, subjects will be asked a series of questions related to their education, occupational status, size and annual income of their household. These data will be used to create a measure for SES that categorizes subjects into low, moderate and high SES (King et al., 2011). The method used to create SES tertiles will be described in the SAP.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

The FDA MRTP guidelines specify the following definition for adverse events for tobacco products (FDA, 2012a):

An AE is any health-related event associated with the use of a tobacco product in humans, which is adverse or unfavorable, whether or not it is considered related to the tobacco product, as defined by the MRTP guidelines.

8.1.2 Serious Adverse Events

An SAE is defined as, but not limited to, any untoward medical occurrence that:

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

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

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

8.2 Assessment of Adverse Events

The Investigator is responsible for obtaining, assessing, and documenting all AEs during the study.

8.2.1 Collection of Information

Adverse event information will be collected from the time of signature of the ICF onwards until the End-of-Study Visit (EOS) either by the Investigator via spontaneous reporting or by the use of consistent, open, non-directive questions from study site staff (e.g., "Have you had any health problems since the previous visit/How have you been feeling since you were last asked?"). At the discretion of the Investigator, the collection of AE information may also be triggered from his/her review of the subject questionnaires and the VAS. However, the main source for AE collection will be face-to-face interview(s) with the subject.

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

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

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

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

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

8.2.2 Period of Collection

From the signature of the ICF onwards until EOS, all AEs (includes SAEs) will be collected by the study site staff as described below.

8.2.2.1 Screening Period

All existing health conditions identified during the Screening period will be recorded as concomitant disease and the subject's eligibility for admission to the study will be reviewed. Any AEs which occur during the screening period will be captured by the study site staff and assessed by the PI in order to establish relationship or relatedness in respect to study procedures. Only the study procedures-related AEs will be reported in the clinical study report and in accordance with respective regulatory guidelines.

8.2.2.2 Admission Day until End of Study

From Admission onwards until Day of Discharge, all AEs will be actively collected by the study site staff.

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

During the safety follow-up period new AEs and/or SAEs will be recorded after spontaneous reporting by the subject. SAEs will be reported by the Investigator as described in this document and the Safety Management Plan. Any ongoing AEs/SAEs during the safety follow-up period will be actively followed up by the site until they have been resolved, stabilized (i.e., no worsening of condition), or an acceptable explanation has been found.

At the end of the safety follow-up period all ongoing AEs/SAEs will be followed up by the Investigator or its delegate on behalf of the sponsor (see Section 8.3) until they have resolved, stabilized (i.e., no worsening of condition), or an acceptable explanation has been found.

8.2.3 Intensity of Adverse Event

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

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

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

Severe: The AE is incapacitating and requires medical intervention.

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

According to the CIOMS VI Working Group, there are no definitive methods for distinguishing most adverse reactions (i.e., events that are causally attributed to the IP) from clinical AEs that occur as background findings in the population and have only temporal association with the IP and reference point product.

In general, all AEs and/or SAEs will be assessed by the Investigator as either ‘related’ or ‘not related’ to IP or reference point product as described below. In addition to the assessment of

the relationship of the clinical event to the IP, the Investigator shall document a potential relationship of the clinical event to any particular study procedure.

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

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

8.2.5 Expectedness

An AE will be regarded as 'unexpected' if its nature or severity is not consistent with information already known about the IP or reference point product, and/or has not been previously observed and is not listed in the current IB. The IB provides further detail on signs or symptoms that might be expected with the use of the IP, including information relating to device malfunction or misuse.

NNS-related AEs listed on the provided product label are included in Appendix 4.

8.3 Reporting and Follow-Up of Serious Adverse Events

SAEs reported or observed during the study after signature of the ICF until the end of the safety follow-up period (i.e., up to 7 days after study Discharge) whether or not attributable to the IP, to any other medication or to any study procedures, or any SAE related to the product and spontaneously reported after the safety follow-up must be reported by the Investigator or other study site staff **within 24 hours after first awareness by any party involved in the study** to [redacted] and to the Sponsor.

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

[redacted]

Fax number: [redacted]

Phone number: [redacted]

E-mail: [redacted]

Address: [redacted]

Switzerland

Sponsor: Contact: [redacted], MD, Medical Safety Officer	**Phone number:**	+41 [redacted]
	Mobile:	+41 [redacted]
	E-mail:	[redacted]@pmi.com
	Address:	Philip Morris Products S.A. R&D Innovation Cube T3551 Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

The Investigator is responsible for local reporting (e.g., to the IRB) of SAEs that occur during the study, according to local regulations.

Any SAE will be reported to the CTP's Office of Science within 15 business days after the report is received by the Sponsor.

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

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

All SAEs will be followed up by the Investigator or designee and/or [redacted] until resolution or until the Investigator considers the event to be stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

The SAE report form to be used in this study is provided as a separate document. All SAEs will be recorded on the relevant eCRF page, in addition to the SAE report form.

8.4 Reporting of Other Events Critical to Safety Evaluations

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for clinical relevance. If the Investigator considers

the abnormal result to be of clinical relevance, then it must be recorded as a concomitant disease at Screening, or if not present at Screening, as an AE during the study.

The grading scheme shown in (reference to the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] version 4.03) will be used by the Investigator to assess abnormal laboratory AEs as follows:

- All Grade 1 abnormal laboratory values will be evaluated by the Investigator with respect to baseline value and clinical relevance. If considered to be clinically relevant, the Investigator must report it as an AE. All Grade 2 and higher abnormal laboratory values must be reported as or linked to an AE/concomitant disease.

- If a subject has Grade 2 and higher abnormal laboratory values at Screening it is at the discretion of the Investigator to enroll the subject or not. This decision must be documented in the source documentation and captured in the eCRF.

- If there is any worsening in grade from Grade 2 and above during the study, the Investigator must report this worsening as an AE.

- Where there is no grading available, the abnormal laboratory value will be evaluated by the Investigator and assessed for clinical relevance. If considered to be clinically relevant, the Investigator will report it as an AE.

- Any other abnormal clinical laboratory result (including those that are not part of the core safety assessments) can, at the discretion of the Investigator, be reviewed and assessed. Even if they do not meet the criteria of the CTCAE grading scheme (please see above), the Investigator may consider them to be of clinical relevance and, if they are, must report them as AEs.

- In general, laboratory values will be recorded as ‘increased <lab parameter>’ or ‘decreased <lab parameter>’ to ensure consistency of recording/coding.

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

8.5 Reporting and Follow–Up of Pregnancies

Pregnancies detected during the Screening Period and prior to first THS 2.2 Menthol use, the subject will be considered as a screen failure and removed from the study. No Pregnancy Form will be filled, however the diagnosed pregnancy must be captured in the Screen Failure eCRF.

All pregnancies occurring after signature of the ICF/subject information sheet and diagnosed after first exposure to the IP until completion of the study must be reported by the Investigator.

Any pregnancy potentially associated to exposure to the IP, including pregnancies spontaneously reported to the Investigator after the end of study, must be reported by the Investigator and followed-up. Potential association with exposure to the IP is defined as the conception date being calculated to have been before the date of last exposure to the IP.

The Investigator will complete a Pregnancy Form (provided as a separate document) for all pregnancies diagnosed (including positive urine pregnancy tests).

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

[redacted] will follow up pregnancies only if they were detected after first product use (i.e., after THS 2.2 Menthol test on Admission Day). If pregnancies are to be followed up, they will be followed up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination). Any pregnancy complication, adverse pregnancy outcome, or maternal complications will be recorded.

The Investigator is responsible for informing the IRB of any pregnancy that occurs during the study and its outcome, according to local regulations.

8.6 Adverse Events Leading to Withdrawal

Subjects who are withdrawn from the study because of an AE will undergo the EOS procedures, as described for the day of Discharge, as soon as possible and will enter the period of safety follow-up. The Investigator and/or [redacted] will follow up these AEs until they have resolved, stabilized (i.e., no worsening of condition), or an acceptable explanation has been found.

8.7 Investigational Device Misuse

Any occurrences of the THS Tobacco Stick Holder or Charger misuse (use not in accordance with its label and instruction) by a subject, will be documented by the Investigator or his/her designated staff using a Device Issue Log.

Investigational device misuse may result in use-related hazards.

Use-related hazards are derived from the US Food and Drug Administration Medical Device Use-Safety Guidance (FDA, 2012b):

- Hazards caused specifically by how a device is used

- Unanticipated use scenarios (e.g., modification of Charger, applying any chemicals, using conventional cigarettes, mechanical damage of the device, etc.) that result in hazards must be documented and reported by the Investigator or designee.

According to FDA Medical Device Regulation, data should be collected regarding the use-related hazards that have occurred with the device and when information pertaining to device use safety is extensive, it is helpful to provide it in summary form that highlights the most important issues, considerations, resolutions, and conclusions. The level of detail of device use documentation submitted should be consistent with the level of concern of use-related hazards for the device.

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

The process of capturing, assessing, and reporting is described in details in the Safety Management Plan.

8.8 Investigational Device Malfunction

Any occurrences of malfunction of the THS Tobacco Stick Holder or Charger will be documented by the Investigator or his/her designated staff using a Device Issue Log.

Furthermore, any malfunctions of the THS Tobacco Stick Holder or Charger unit that lead 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 1. The time points shown are to be considered the time of assessment for the first subject. As not all subjects can be treated at the same time, a short time window will be implemented for subsequent subjects. Measurements not conducted at the exact time point, but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given time point.

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

9.1 Screening Visit

The Screening Visit will be performed within 4 weeks (Day -29 to Day -2) prior to Admission (Day -1). Subjects will attend the investigational site in at least a 10-hour fasting state for clinical laboratory to be assessed.

The following assessments will be performed at the Screening Visit (Table 4) (the sequence of the assessment will be at the discretion of the site but all of them must be done after signature of the ICF:

Table 4. Time Schedule – Screening

Time	Blood sample	Procedures	Additional information
Start of procedure			
		Informed consent	
		Advice on the risks of smoking and debriefing	
		Demographic data	
		Smoking history	
		Willingness to quit smoking in the next 3 months	
		Readiness to accept interruptions of smoking for up to 4 days	
		FTND questionnaire	
		Prior medication (4 weeks prior to screening visit)/concomitant medication	

	Medical history /concomitant diseases	
	Vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate)	At least 5 min in supine position prior to measurement
	Height, weight, including calculated BMI	
√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	In at least 10 hours of fasting
√	Serology for HIV and Hepatitis B and C	
	Identification of current mCC brand	
	Urine drug screen	
	Alcohol breath test	
	Urine pregnancy test for all female subjects	
	THS 2.2 Menthol and NNS product demonstration	
	Spirometry without short-acting bronchodilator first, and then with	To be done at least 1 hour after smoking
	ECG	At least 10 min in supine position prior to recording
	AE/SAE questioning	If the Screening Visit is performed on two separate days the AE/SAE questions will be asked again
	Physical examination	
	Chest X-ray (if not performed 6 months prior to Screening)	
	Urine cotinine screening test	
	Inclusion/exclusion criteria	

Abbreviations: AE = Adverse event; BMI = Body mass index; mCC = menthol conventional cigarette(s); ECG = Electrocardiogram; FTND = Fagerström Test for Nicotine Dependence (revised version); HIV = Human immunodeficiency virus; NNS = Nicotine nasal spray; SAE = Serious adverse event; THS 2.2 Menthol = Tobacco Heating System 2.2 menthol

9.2 Admission

The following assessments will be performed at Admission (Day -1) (Table 5):

Table 5. Time Schedule – Day -1 Admission

Time	Blood sample	Procedures	Additional information
Start of procedure			
		AE/SAE recording, concomitant medication	All day
		Advice on the risks of smoking and debriefing	
		Readiness to accept interruptions of smoking for up to 4 days	
	√	*trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma	The subject should not have smoked in the morning until this assessment Must be done prior to smoking
		Spirometry	Has to be done prior smoking
6:30 AM		Beginning of smoking period	
		Urine pregnancy test for all female subjects	
	√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	In at least 10 hours of fasting
		Urine cotinine screening test	
		Urine drug screen	
Prior to 10:00 AM		Breakfast	
Prior to 11:30 AM		Vital signs	At least 5 min in supine position prior to measurement
Prior to 11:30 AM		Physical examination, weight and calculated BMI	
Prior to 11:30 AM		Identification of current mCC brand	
Prior to 11:30 AM		Smoking history	
Prior to 11:30 AM		Alcohol breath test	
Prior to 11:30 AM		CO breath test	
Prior to 2:30 PM		Lunch	

afternoon	Snacks	
4:30 PM-6:00 PM	Product test for THS 2.2 Menthol and NNS	The THS 2.2 Menthol test should be done first and then the NNS test
4:30 PM-6:00 PM	Inclusion/exclusion criteria	
4:30 PM-6:00 PM	Enrolment	
In the evening prior to 9:00 PM	Dinner	
11:00 PM	End of smoking period	

Abbreviations: AE = Adverse event; BMI = Body mass index; CC = conventional cigarette(s); CO = Carbon monoxide; CYP2A6 = Cytochrome P450 2A6; NNS = Nicotine nasal spray; SAE = Serious adverse event; THS = Tobacco Heating System

9.3 Investigational Period

9.3.1 Days of Smoking Abstinence (Day 0 and Day 2)

On the days of smoking abstinence (Day 0 and Day 2) the following assessments will be performed (Table 6 and Table 7):

Table 6. Time Schedule – Day 0 Washout

Time	Blood sample	Procedures	Additional information
Start of procedure			
		Nicotine abstinence	All day
		Support during nicotine abstinence as required	All day
		AE/SAE recording, concomitant medication	All day
		Randomization	At any time of the day
06:30AM-09:00 AM		Assessment of cough	
Prior to 10:00 AM		Breakfast	
8:00 AM-9:30 AM		CO breath test	
10:00 AM-11:30 AM		Vital signs	At least 5 min in supine position prior to measurement
12:00 PM-1:30 PM		CO breath test	
Prior to 2:30 PM		Lunch	

4:00 PM-5:30 PM	CO breath test
Afternoon	Snacks
In the evening prior to 9:00 PM	Dinner
8:00 PM-9:30 PM	CO breath test

Abbreviations: AE = Adverse event; CO = Carbon monoxide; SAE = Serious adverse event.

Table 7. Time Schedule – Day 2 Washout

Time	Blood sample	Procedures	Additional information
Start of procedure			
		Nicotine abstinence	All day
		Support during nicotine abstinence as required	All day
		AE/SAE recording, concomitant medication	All day
		Socio-economic status	At any time of the day The questionnaire will be administered by a trained interviewer
	√	Plasma nicotine PK sample	24 hrs after T_0 of Day 1 +5 min
		Assessment of cough	24 hrs after T_0 of Day 1 minus 5 min
Prior to 10:00 AM		Breakfast	
8:00 AM-9:30 AM		CO breath test	
10:00 AM-11:30 AM		Vital signs	At least 5 min in supine position prior to measurement
12:00 PM-1:30 PM		CO breath test	
Prior to 2:30 PM		Lunch	
4:00 PM-5:30 PM		CO breath test	
Afternoon		Snacks	
In the evening prior to 9:00 PM		Dinner	
8:00 PM-9:30 PM		CO breath test	

Abbreviations: AE = Adverse event; CO = Carbon monoxide; PK = Pharmacokinetic; SAE = Serious adverse event; T = Time point.

9.3.2 Days of Single Use (Day 1 and Day 3)

On the days of single use (Day 1 and Day 3), the following assessments will be performed (Table 8):

Table 8. Time Schedule – Day 1 and Day 3 Single Use

Time	Blood sample	Procedures	Additional information
Start of procedure			
		Optional: light snacks prior to first blood draw of the day	
		AE/SAE recording, concomitant medication	All day
		Support for smoking abstinence as required	All day
		Craving questionnaire (QSU-brief)	In all subjects: First assessment within 15 min prior to T_0, 9 assessments thereafter in relation to T_0: 15 min, 30 min, 45 min, 60 min, 2 hr, 4 hrs, 6 hrs, 9 hrs, and 12 hrs after T_0 with a time window of 10 minutes each.
	√	Plasma nicotine sample	First sample within 15 min prior to T_0, 15 samples thereafter in relation to T_0: T1 after 2 min +1 min, T2 after 4 min +1 min, T3 after 6 min +1 min, T4 after 8 min +1 min, T5 after 10 min +1 min, T6 after 15 min +2 min, T7 after 30 min +2 min, T8 after 45 min +2 min, T9 after 60 min +3 min, T10 after 2 hrs +5 min, T11 after 4 hrs +5 min, T12 after 6 hrs +5 min, T13 after 9 hrs +5 min, T14 after 12 hrs +5 min, and T15 after 24 hrs +5 min) Cotinine in addition to nicotine will be measured in plasma in all time points but only the data for the three following time points: prior T_0, $T_{0+12\ hours}$ (T_{14}), $T_{0+24\ hours}$ (T_{15}) will be used for analysis.

	√	COHb blood sampling	Five blood samples to be taken, first sample within 15 min prior to T_0, then after 15 min +2 min, 60 min +3 min, 4 hrs +5 min, 12 hrs +5 min
		CO breath test	First test to be done within 15 min prior to T_0
		Assessment of cough	Has to be done prior to product use
6:00 AM-9:00 AM		Start of single product use	
Prior to 10:00 AM		Breakfast	
10:00 AM-11:30 AM		Vital signs	At least 5 min in supine position prior to measurement
10:00 AM-11:30 AM		ECG	At least 10 min in supine position prior to recording
12:00 PM-1:30 PM		CO breath test	
Prior to 2:30 PM		Lunch	
4:00 PM-5:30 PM		CO breath test	
Afternoon		Snacks	
Prior to 9:00 PM		Dinner	
8:00 PM-9:30 PM		CO breath test	
8:00 PM-11:00 PM		Product evaluation questionnaire (MCEQ; only in sequence 1 and 2)	
		Collection of used Menthol Tobacco Sticks and CC butts and NNS	After the product use

Abbreviations: AE = Adverse event; CC = conventional cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; ECG = Electrocardiogram; MCEQ = Modified Cigarette Evaluation Questionnaire; NNS = nicotine nasal spray; QSU-brief = Questionnaire of Smoking Urges; SAE = Serious adverse event; T = Time point

9.4 Day of Discharge

The following assessments will be conducted prior to the time of Discharge on Day 4 (or after a subject is prematurely withdrawn from the study) (Table 9):

Table 9. Time Schedule – Day 4 Discharge

Time	Blood sample	Procedures	Additional information
Start of procedure			
		AE/SAE recording, concomitant medication	All day
	√	Plasma nicotine: PK sample	24 hrs since T_0 of Day 3 +5 min
		Assessment of cough	24 hrs since T_0 of Day 3 +5 min
	√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	At to be done in at least 10 hours of fasting
		Spirometry	Has to be done prior to smoking
Prior to 10:00 AM		Breakfast	
Prior to discharge		Urine pregnancy test for all female subjects	
Prior to discharge		Vital signs	At least 5 min in supine position prior to measurement
Prior to discharge		CO breath test	Irrespective of smoking
Prior to discharge		Physical examination, weight and calculated BMI	
Prior to discharge		Advice on risk of smoking and debriefing	
		Time of discharge	

Abbreviations: AE = Adverse event; BMI = Body mass index; CO = Carbon monoxide; PK = Pharmacokinetic; SAE = Serious adverse event; T = Time point

9.5 Safety Follow-up Period

All subjects participating in the product trial on Day -2 and are not enrolled into the study will enter a 28-day safety follow-up period.

After the time of Discharge at Day 4 (or if prematurely withdrawn from the study), subjects will enter a 7-day safety follow-up period.

During the 7-day safety follow-up period, there will be spontaneous reporting by the subject of new AEs and new SAEs. Any ongoing AEs/SAEs will be actively followed up by the site.

Any AEs or SAEs that are ongoing at the end of the 7-day safety follow-up period will be handled as described in Section 8.2.2.

9.6 Early Termination Procedures

The Day of Discharge assessments will be performed as early termination procedures (see Section 9.4). Early termination procedures will be the same as those described in the day of Discharge.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

A Clinical Research Associate ("Monitor") from an independent CRO not involved with the study site will be responsible for the monitoring of the study. Monitoring will be performed according to the study CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

The Investigator shall permit the Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor so that entries in the eCRFs may be verified. The Investigator, as part of their responsibilities, is expected to ensure that the study adheres to GCP requirements.

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

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

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

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

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

The Investigator, or a designated member of the Investigator's staff, must be available during the monitoring visit to review the data and resolve any queries, and to allow direct access to the subject's records for source data verification.

10.2 Training of Staff

A formal meeting (Investigator's meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training in the relevant systems and other study-specific procedures. The activities of the Investigator's meeting will be described in the monitoring plan.

In addition to the Investigator's meeting, the Principal Investigator 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 to the staff involved in a timely manner. The Principal Investigator will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

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, and any applicable regulatory requirements. The Investigator will contact the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the Investigator understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All Data Management Activities will be described in detail in the Data Management Plan and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

With the exception of the subject-reported outcome data, all results from the clinical assessments will be recorded in the Source Documents by the Investigator or their authorized designee(s) and then captured in the eCRFs at the study site. The subject questionnaires and the VAS will be entered by the subject directly in the electronic patient-reported outcomes device or in a paper copy. Trained study personnel will be responsible for capturing the data from the observations, tests and assessments specified in the protocol in the source documents and then transferring the data into the eCRF, in accordance with the Case Report Form Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring and available when required. The eCRF must be signed by the Investigator to attest that the data contained in the eCRF are true and accurate. Any corrections 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 study site by the Clinical Research Associate. 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 informed consent form.

11.1.2 Protocol Deviations

Protocol deviations are defined as those deviations from any procedure as defined in this document, including but not limited to, as any violation of inclusion/exclusion criteria, mis-randomizations, use of any nicotine or tobacco-containing product other than the assigned product during each of the exposure period, use of any nicotine tobacco-containing product during wash-out days, assessments not performed or performed outside the scheduled time windows, or use of estrogen or other drugs that are known to affect CYP2A6 activity.

All protocol deviations will be entered into the Clinical Trial Management System (CTMS) or other approved format.

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.

Individual entries for protocol deviations that are recorded in the CTMS, or other approved format, following site monitoring and other manual reviews, will be reviewed against the individual data points in the eCRF database but will not be formally reconciled with the eCRF database (e.g., their description or occurrence date). The overall procedure for managing protocol deviations are described in the SOPs of the CRO Data Management Team. All deviations will be reviewed periodically, as determined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.2 Data Handling

All study data will be managed by the Data Management Team at the CRO. 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 Data Management Plan, to be reviewed and approved by the Sponsor, prior to the start of the study. This document will describe, in detail, the procedures and processes related to Data Management.

All data of all subjects successfully enrolled, as well as subjects who failed screening, and/or experienced an AE during the study (from time of signing the informed consent form to the end of the safety follow-up period), will be captured and stored in the study database.

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

11.2.1 Data Validation

The data will be validated as defined in the Data Management Plan and Data Validation Specifications. Discrepancy lists will be generated electronically, as necessary.

Data queries will be raised for discrepant or missing data. All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

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

Medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Adverse events:	MedDRA®
Medications:	WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical classification system
THS 2.2 device issues and/or malfunctions:	C54451/Medical_Device_Problem_Codes_FDA_CDRH (FDA, 2012b)

11.2.3 Database Lock

When all outstanding Data Management issues have been resolved and all validation, quality review and cleaning activities are complete, the database or selected data is/are declared soft-locked. Access to change data in the soft-locked database or to change selected data at this time is limited.

After data review by the Sponsor, resolution of all raised queries and QC of the changed data, the database or selected data thereof will be declared locked upon Sponsor approval, as applicable.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the Data Management and Statistical Team at the CRO. Any of those changes must be documented in the database log file.

After study completion, the study database will be transferred to the Sponsor in the format specified in the Data Management Plan in the Clinical Data Interchange Standards Consortium Study Data Tabulation Model Data Structure Specifications.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

An incomplete block design will be adopted in this study with every subject being exposed to 2 out of the 3 study products (mCC, THS 2.2 Menthol, and NNS) to allow comparisons between THS 2.2 Menthol and mCC in Group-1, and between THS 2.2 Menthol and NNS in Group-2.

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

12.1.1 Stratification Criteria

For analysis, the following stratification criteria will be used:

- Sex (male and female).
- mCC nicotine level at Admission (ISO nicotine levels ≤ 1 mg or >1 mg).

In addition, for the safety data, the analysis will be stratified by sequence and by study periods (Screening, product test, product exposure, and safety follow-up period).

12.1.2 Definitions for Statistical Data Analysis

Unless otherwise stated, for the purposes of statistical analyses, baseline is defined as the last available time point prior to T_0 on Day 1, from 6:00 AM to 9:00 AM.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by sequence and subject, unless otherwise specified.

Descriptive statistics for continuous variables (number of subjects [n], number and percent of subjects with missing data, mean, standard deviation, median, first and third quartiles, minimum and maximum for continuous data, and the n and absolute and relative (%) frequency for categorical data) will presented by exposure and overall at each time point, where applicable.

Descriptive statistics for PK parameters will also include the geometric mean and coefficient of variation (CV).

Baseline, admission, and screening data (i.e., anything prior to product exposure) will be summarized by sequence and overall where appropriate.

12.1.4 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.

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), i.e., preceded by a ">", for example ">xx," the numerical xx will be used for calculation and reporting in summary tables. The number of values below LLOQ or above ULOQ will be presented in each summary table.

12.1.5 Significance Level for Inferential Analysis

For all endpoints, unless otherwise stated, statistical tests will be two-sided and conducted at the 5% significance level and all quoted confidence intervals will be two-sided 95% confidence intervals.

No formal adjustment of the test-wise alpha level for multiple testing is necessary, as no claim will be made based on the outcome of the individual tests.

12.2 Determination of Sample Size and Power Consideration

A total of 62 subjects will be randomized. This is calculated by adding up sample sizes separately estimated for each analysis.

A total of 44 subjects are needed to estimate the mean C_{max} parameter ratio between THS 2.2 Menthol and mCC with a 90% probability of obtaining a margin of error (95% confidence interval) of at most ±20%, assuming that THS 2.2 Menthol have a nicotine PK profile similar to mCC (C_{max} ratio equal to 1.00) and a 10% dropout rate.

A total of 18 subjects are needed to estimate the mean C_{max} parameter ratio between THS 2.2 Menthol and NNS with a precision allowing for the lower bound of the 95% confidence interval exceeding 1.00, with 90% power and assuming a 10% dropout rate. The anticipated geometrical C_{max} ratio between THS 2.2 Menthol and NNS is 1.55, based on data reported by Gourlay and Benowitz, 1997, and Johansson et al., 1991.

The estimates for the within-subject CV for nicotine Cmax (36%) and AUC(0-last) (21%) are based on the data collected in the ZRHX-PK-02 clinical study (ZRHX-PK-02, 2012) comparing the nicotine PK profiles of Tobacco Heating System 2.1, the predecessor of THS 2.2 (non-menthol) and CC. In the absence of data comparing THS Menthol and NNS, the same CVs were assumed for the calculation of the sample size related to the THS 2.2 Menthol:NNS comparison.

Sample size calculations were conducted using SAS® version 9.2 for the 95% CI of the mean differences between paired observations (proc power onesamplemeans) in the natural log scale (Senn, 2002). The SAS® implementation of the method published by Beal, 1989 was adopted to estimate the probability of obtaining at most the target confidence interval of ± 20%.

12.3 Analysis Populations

All analyses will be based on actual product exposure. All endpoints (other than safety) will be analyzed using the PK Analysis sets. Safety will be analyzed using the safety population.

12.3.1 PK Populations

The analysis populations for the PK endpoints are composed of two analysis sets to allow the comparison between THS 2.2 Menthol and NNS separately from the comparison between THS 2.2 Menthol and mCC.

The PK populations consist of all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations (to be defined in the SAP) will be included in the PK analysis sets.

12.3.2 Safety Population

The safety population consists of all the subjects who give informed consent and have at least one exposure to THS 2.2 Menthol (including the product test at Admission Day).

12.4 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be reported for the PK and safety populations. Appropriate summary statistics will be provided as described in Section 12.1.3.

12.5 Primary Endpoints

12.5.1 Primary Endpoint Analysis Variables

Nicotine PK parameters will be derived from plasma nicotine versus time data using a non-compartmental technique. In particular:

C_{max} Maximum observed plasma concentration. C_{max} will be reported as long as there is at least one quantifiable concentration post-exposure

$AUC_{(0\text{-last})}$ Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration (linear trapezoidal method).

12.5.2 Baseline Comparability

Not applicable.

12.5.3 Descriptive Analysis

Primary endpoints will be summarized as described in Section 12.1.3.

An analysis of variance (ANOVA) will be conducted on $AUC_{(0\text{-last})}$ and C_{max} endpoints in the natural logarithmic scale. The model will include terms for sequence, subjects within sequence, period, and exposure group as fixed effect factors. The results of this analysis for each of $AUC_{(0\text{-last})}$ and C_{max} are presented in terms of adjusted geometric least square means and 95% confidence intervals for the THS 2.2 Menthol:mCC and THS 2.2 Menthol:NNS ratios.

This approach is consistent with the guidelines in the European Medicines Agency's guidelines for bioequivalence investigations (EMA, 2008) and FDA's Center for Drug Evaluation and Research (FDA, 2001). Carry-over effect will not be tested, as it cannot be statistically distinguished from the interaction between treatment and period in a 2x2 crossover design (ICH E9, 1998).

A sensitivity analysis will be conducted should there be 20% or more missing PK parameter values by repeating the above analyses using mixed effects ANOVA model in the natural log scale with a restricted maximum likelihood method to estimate mean differences and variances as suggested by FDA (FDA, 2001). Subjects within sequence will be used as random effects and fixed effects are period, sequence, and product exposure. To evaluate the sensitivity to the distributional assumptions, point and interval estimates will also be

estimated by means of the percentile bootstrap technique, which uses 2000 bootstrap samples to preserve the number of subjects per sequence.

12.5.4 Confirmatory Analyses

Given that the objective of this study is to determine the point estimate and precision of the ratio of THS 2.2 Menthol:mCC for C_{max} and $AUC_{(0\text{-last})}$, there is no statistical hypothesis to be tested.

12.6 Secondary Endpoints

12.6.1 Secondary Endpoint Analysis Variables

Nicotine PK parameters will be derived as follows:

t_{max} Time to maximum concentration. t_{max} will be reported as long as there is at least one quantifiable concentration post-exposure

$AUC_{(0\text{-t'})}$ Area under the plasma concentration-time curve from start of product use to the subject-specific time of maximum nicotine concentration following singe use of mCC or NNS (linear trapezoidal method)

$AUC_{(0\text{-}\infty)}$ Area under the concentration-time curve from start of product use extrapolated to time of last quantifiable concentration to infinity, according to:

$$AUC_{0\text{-}\infty} = AUC_{0-last} + \left(\frac{C_{last}}{\lambda z} \right)$$

Where C_{last} is the last quantifiable concentration and λ_z is the terminal elimination rate constant

λ_z Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data

$t_{1/2}$ Half-life (terminal elimination), derived as $\ln(2)/\lambda_z$

More details on PK parameter derivations will be provided in the SAP.

Subjective effects of using THS 2.2 Menthol as compared to the mCC and to the NNS will be evaluated by analyzing domain scores of QSU-brief and MCEQ. Full details of questionnaire domain scores derivation will be provided in the SAP.

12.6.2 **Baseline Comparability**

Not applicable.

12.6.3 **Descriptive Analysis**

In general, secondary endpoints will be summarized using the approach described in Section 12.1.3.

The following analyses will be conducted in both Group-1 and Group-2 PK analysis sets:

- The $AUC_{(0-\infty)}$, $AUC_{(0-t')}$, and $t_{1/2}$ will be analyzed using the same approach adopted for the primary endpoints. No statistical analysis will be performed on the elimination rate constant λ_z. Data will be summarized and presented together with 95% CI.
- The Hodges-Lehmann 95% CI estimates for the median t_{max} differences will be presented (Lingling, 2008).
- The use of random effects model is suggested in the context of the analysis of subjective effects of smoking (Shiffman et al., 2004). Mixed effects ANOVA with the same model terms as planned for the sensitivity analysis of the primary endpoints will be adopted for the analysis of analysis of QSU-brief, including all of the different assessment time points as repeated measurements. The analysis will not be adjusted for the assessment prior to T_0 (Fleiss et al., 1985).
- Levels of exhaled CO and of blood COHb will be summarized by means of descriptive statistics reported by exposure. Analysis of COHb levels will be conducted using a mixed model for repeated measures, the same approach as for the QSU-brief.
- Cotinine levels will be summarized by means of descriptive statistics reported by exposure.

The following analyses will be conducted only in Group-1 PK analysis set:

- Mixed effects ANOVA with the same model terms as planned for the sensitivity analysis of the primary endpoints will be adopted for the analysis of the MCEQ domain scores.

The following analyses will be conducted in only Group-2 PK analysis set:

- To test if the time to the maximum nicotine concentration in THS 2.2 Menthol is shorter than in NNS the following hypothesis will be evaluated:

H_0: $X_{THS} - X_{NNS} = 0$ H_A: $X_{THS} - X_{NNS} < 0$

where X_{THS} and X_{NNS} are the median values of the THS 2.2 Menthol and NNS, respectively. t_{max} will be analyzed on the original scale using the Wilcoxon Signed-Rank Test with a type I error $\alpha = 0.025$ (one-sided test), as values are ordinal/discrete, and the assumption of normality may be questionable.

- To determine if the rate and the amount of nicotine absorbed of the THS 2.2 Menthol is higher relative to NNS the following hypothesis will be tested for both C_{max} and $AUC_{(0\text{-last})}$ parameters:

  H_0: $X_{THS} / X_{NNS} = 1.0$ H_A: $X_{THS} / X_{NNS} > 1.0$

  where X_{THS} and X_{NNS} are the adjusted geometrical means of THS 2.2 Menthol and NNS, respectively. H_0 is rejected with a type I error $\alpha = 0.025$ (one-sided test), if the lower bound of the 95% CI for the X_{THS} / X_{NNS} ratio is higher than 1.0.

12.6.4 Confirmatory Analyses

Not applicable.

12.6.5 Safety Endpoints

In general, all safety data will be listed and tabulated on the safety population by sequence, using the approach described in Section 12.1.3. Safety variables collected during exposure periods will also be reported by product exposure.

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

The number and percentage subjects with AEs and SAEs will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to withdrawal, 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.

The number and percentage of subjects with clinical findings will be tabulated by sequence for laboratory parameters. Shift tables showing change from baseline of clinical findings will be provided for: ECGs, physical examinations, and laboratory parameters (both shifts in

normal ranges and toxicity grades). Descriptive statistics will be summarized by visit and change from baseline for laboratory parameters, ECG, respiratory symptoms, and vital signs.

12.7 Exploratory Analyses

There are no planned exploratory analyses.

12.8 Interim Analysis

There are no planned interim analyses.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

13.1.1 Investigator

Principal Investigator:	James L. Borders, MD Central Kentucky Research Associates 3475 Richmond Road Third Floor Lexington, KY 40509 USA Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Site contacts:	[redacted] [redacted]

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland. Tel: +41 (58) 242 2111 Fax: +41 (58) 242 2811
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[redacted] Medical Writer	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]*@pmi.com*
[redacted], PhD Clinical Study Manager	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]*@pmi.com*

13.1.3 **Other Responsibilities**

Any SAEs or pregnancies will be handled by:

[redacted]

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

13.2 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. A statement to this effect will be written in the

information provided to the subject. An agreement to disclose any such information will be obtained from the subject in writing and signed by the subject, in compliance with all local and national data protection and privacy legislation.

The anonymity of subjects participating in this study will be maintained. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on eCRFs 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 an 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 study information sheet and ICF) must be maintained in confidence by the Investigator. 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 Documentation

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

13.4 Record Retention

All records of data, source data, and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans, X-rays, and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study, and the actions taken will be maintained by the Investigator/study site for the study, as required by ICH GCP and any other applicable local or national regulations. For X-rays, at least the radiologist's assessment is required as source documentation. If the actual image is available it can be stored on a CD as well.

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 (ICH Guideline for Good Clinical Practice E6 (R1), July 1996).

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 the 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 (if applicable), and Enrolment Log (if applicable)
- Record of all communications between the Investigator and the IRB, composition of the IRB
- Record of all communications/contact between the Investigator, 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, CVs, and their signatures
- Investigator Logs
- eCRFs, 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., chest X-rays, ECGs, consultation reports, physical examination, and 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 Investigator/study site as to when these documents no longer need to be retained.

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

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

The Investigator must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If an Investigator is unable to meet this obligation, they must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

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

13.5 Clinical Study Report

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

The CSR will be written based on standards of the ICH Guideline for the Structure and Content of Clinical Study Reports. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IRB will be complied with as requested by local requirements.

13.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor. In addition, the Investigators must agree with the Sponsor to commit to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains data, information and trades secretes that are confidential and proprietary to the Sponsor. This document is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor. Disclosure of the content of

this document is allowed only to study personnel, IRB, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations.

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

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Appendix 1 Schedule of Events

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge [k]	Safety follow-up [l]
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Informed consent	●							
Advice on the risks of smoking and debriefing	●	●					●	
Inclusion/exclusion criteria	●	●						
Enrolment		●						
Randomization			●					
Product use				●		●		
Support during periods of reduced smoking/smoking abstinence (as required)			●	●	●	●		
Product demonstration of THS 2.2 Menthol and NNS	●							
Product test for THS 2.2 Menthol and NNS		●						
Identification of current CC brand	●	●						
Smoking history	●	●						
Willingness to quit smoking in the next 3 months								
Readiness to abstain from smoking for up to 4 days	●	●						
Demographics [a], medical history, concomitant diseases	●							
Socio-economic questionnaire					●			
Prior medication [b] / Concomitant medication	●	●	●	●	●	●	●	●

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge [k]	Safety follow-up [l]
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Physical examination, body height, weight and related BMI [c]	●	●					●	
Vital signs [d]	●	●	●	●	●	●	●	
ECG	●			●		●		
Spirometry	●	●					●	
Chest X-ray [e]	●							
B/U: Hematology, clinical chemistry, urine analysis	●	●					●	
B: Serology	●							
U: Urine drug screen, urine cotinine screen	●	●						
Alcohol test	●	●						
U: Pregnancy test (all females)	●	●					●	
Collection of used Tobacco Sticks and CC butts				●		●		
B: Plasma nicotine [f]				●	●	●	●	
B: COHb [g]				● (5x)		● (5x)		
CO breath test [h]		● (1x)	● (4x)	● (4x)	● (4x)	● (4x)	● (1x)	
trans-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma		●						
FTND questionnaire	●							
QSU–brief questionnaire [i]				●		●		
MCEQ (modified version, only after THS 2.2 and CC use				●		●		

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge [k]	Safety follow-up [l]
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Cough assessment [j]			●	●	●	●	●	
AE/SAE recording	●	●	●	●	●	●	●	●

Abbreviations: AE = Adverse event; BMI = Body mass index; mCC = Menthol conventional cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP2A6 = Cytochrome P450 2A6; ECG = Electrocardiogram; FTND = Fagerström Test for Nicotine Dependence (revised version); MCEQ = Modified Cigarette Evaluation Questionnaire; NNS = Nicotine nasal spray; QSU-brief = Questionnaire of Smoking Urges-brief; SAE = Serious adverse event; THS 2.2 = Tobacco Heating System 2.2.

B : Blood sample required.

U : Urine sample required.

a: Sex, date of birth/age, race.

b: Prior medication at Screening and the 4 weeks prior to Screening.

c: Including height (only at Screening), body weight, and calculated BMI.

d: Systolic and diastolic blood pressure, pulse rate, respiratory rate.

e: Pre-study chest X-ray (anterior-posterior and left lateral views) to be used, if performed within 6 months prior to Screening.

f: Nicotine blood samples to be taken as follows:

Single use: A total of 16 blood samples will be taken. The first blood sample will be taken within 15 minutes prior to the product use. Thereafter in relation to T_0, blood will be drawn at the following time points: T_1 after 2 minutes, T_2 after 4 minutes, T_3 after 6 minutes, T_4 after 8 minutes, T_5 after 10 minutes, T_6 after 15 minutes, T_7 after 30 minutes, T_8 after 45 minutes, T_9 after 60 minutes, T_{10} after 2 hours, T_{11} after 4 hours, T_{12} after 6 hours, T_{13} after 9 hours, T_{14} after 12 hours, and T_{15} after 24 hours.

Cotinine in addition to nicotine will be measured in plasma in all time points but only the data for the three following time points: prior T_0, $T_{0 + 12\ hours}$ (T_{14}), $T_{0 + 24\ hours}$ (T_{15}) will be used for analysis..

g: COHb blood samples to be taken as follows:

Single use: A total of 5 blood samples will be taken. The first sample within 15 minutes prior to T_0 (start of single product use); thereafter in relation to T_0 at 15 minutes, 60 minutes, 4 hours, and 12 hours

h: A CO breath test will be conducted once on Day -1 and Day 4. On Day 1, Day 2, Day 3, and Day 4, the first test per day will be performed within 15 minutes prior to T_0 (T_0 = start of first product use) and the three other test will be conducted as described in section 9. On the wash-out days (Day 0 and Day 2), it will be conducted 8:00 am-09:30 am. The three other test will be conducted as described in section 9.

i: QSU–brief will be assessed as follows:

Single use: The QSU-brief at single use study days in all subjects.

The first assessment within 15 min prior to T0, 9 assessments thereafter in relation to T0: 15 min, 30 min, 45 min, 60 min, 2 hr, 4 hrs, 6 hrs, 9 hrs, and 12 hrs after T0 with a time window of 10 minutes each.

j: Visual analogue scale, three Likert scales, and one open question.

k: All examinations listed at the Day of Discharge should also be conducted in subjects terminating the study early and all subjects who have tried the product at admission but are not enrolled.

l: Spontaneous reporting of new AEs/SAEs by the subject and active follow-up of ongoing AEs/SAEs by the site.

Appendix 2 Participating Laboratories

Participating laboratories for blood samples testing will be decided prior to the Investigator Meeting and site initiation. Safety laboratory samples will be tested at a local laboratory.

Appendix 3 Investigational Product and Instructions for Use

The product user guide will be provided as a separate document.

Appendix 4 Product Label for the NNS Product: Adverse Events

The NNS product label listing AEs relating to the product can be found at the internet link:

http://www.pfizer.com/products/#nicotrol.

An excerpt of the AE section in the Nicotrol® NS package insert cited above is provided below. Full copies are available in each Nicotrol® NS package and upon request.

*"**Effects of the Spray***

NICOTROL NS and the pepper-containing placebo were both associated with irritant side effects on the nasopharyngeal and ocular tissues. During the first 2 days of treatment, nasal irritation was reported by nearly all (94%) of the patients, the majority of whom rated it as either moderate or severe. Both the frequency and severity of nasal irritation declined with continued use of NICOTROL NS but was still experienced by most (81%) of the patients after 3 weeks of treatment, with most patients rating it as moderate or mild. Other common side-effects for both active and placebo groups were: runny nose, throat irritation, watering eyes, sneezing, and coughing.

The following local events were reported somewhat more commonly for active than for placebo spray: nasal congestion, subjective comments related to the taste or use of the dosage form, sinus irritation, transient epistaxis, eye irritation, transient changes in sense of smell, pharyngitis, paraethesias of the nose, mouth or head, numbness of the nose, or mouth, burning of the nose or eyes, earache, facial flushing, transient changes in sense of taste, hoarseness, nasal ulcer or blister.

Effects of Nicotine

Feelings of dependence on the spray were reported by more patients on active spray than placebo. Drug-like effects such as calming were also more frequent on active spray."

Appendix 5 Abnormal Laboratory Values

ABNORMAL LABORATORY VALUES RATING: SERUM CHEMISTRY PARAMETERS

Serum Chemistry*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Sodium – Hyponatremia (mmol/L) ** (1)	<LLN - 130	-	<130 - 120
Sodium – Hypernatremia (mmol/L) ** (1)	>ULN - 150	>150 - 155	>155 - 160; hospitalization indicated
Potassium – Hyperkalemia (mmol/L)**(1)	>ULN - 5.5	>5.5 - 6.0	>6.0 - 7.0; hospitalization indicated
Potassium – Hypokalemia (mmol/L) ** (1)	<LLN - 3.0	<LLN - 3.0; symptomatic; intervention indicated	<3.0 - 2.5; hospitalization indicated
Glucose – Hypoglycemia ** (1) (mg/dL) (mmol/L)	<LLN – 55; <LLN – 3.0	<55 – 40; <3.0 – 2.2	<40 – 30; <2.2 – 1.7
Blood Urea Nitrogen (BUN) (mg/dL) (2)	23 – 26	27 – 31	>31
Glucose – Hyperglycemia: ** Fasting (1)((mg/dL) (mmol/L)	>ULN – 160; >ULN – 8.9	>160 -250 > 8.9-13.9	>250 – 500; >13.9 – 27.8 Hospitalization indicated
Creatinine increased** (1)	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN
Albumin – Hypoalbuminemia** (1)(g/dL) (g/l)	<LLN – 3; <LLN - 30	<3 – 2; <30 - 20	<2; <20
Total Protein – Hypoproteinemia (2) (g/dL)	5.5 – 6.0	5.0 – 5.4	<5.0
Alkaline phosphatase increased** (1)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN
ALT / AST increased** (1)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN
Gamma-glutamyl transferase (GGT) increased (1)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN
Blood bilirubin increased ** (1)	>ULN – 1.5 x	>1.5 – 3.0 x ULN	>3.0 – 10.0 ULN

	ULN		
Cholesterol high** (1)			
(mg/dL)	>ULN – 300;	>300-400;	>400-500;
(mmol/L)	>ULN – 7.75	>7.75-10.34	>10.34-12.92
Triglycerides - Hypertriglyceridemia (1)			
(mg/dL)	150 – 300;	>300 – 500;	>500 – 1000;
(mmol/L)	1.71 – 3.42	>3.42 – 5.70	>5.70 – 11.40

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

Data Source: (1) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

(2) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

* Those parameters that are not listed do not have grading categories in either the CTCAE or the FDA guidance documents and will therefore be reviewed by the Investigator and only reported as an AE if considered to be clinically relevant.

** Where parameters in this table are listed in both the CTCAE and the FDA guidance documents, and each document has different values within each grading category, the grading in CTCAE guidance document predominates.

ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (Female) – (g/dL) (1)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4
change from baseline value – (g/dL) (1)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0
Hemoglobin (Male) – (g/dL) (1)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4
change from baseline value – (g/dL) (1)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0
Hemoglobin increase – (g/dL) (2)	Increase in >0 – 2 above ULN or above baseline if baseline is above ULN	Increase in >2 – 4 above ULN or above baseline if baseline is above ULN	Increase in >4 above ULN or above baseline if baseline is above ULN
WBC Increase – (cell/mm^3) (1)	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000
WBC Decrease - (cell/mm^3) (2)**	<LLN – 3000; <LLN – 3.0 x 10^{-9}/L	<3000 - 2000; <3.0 – 2.0 x 10^{-9}/L	<2000 - 1000; <2.0 – 1.0 x 10^{-9}/L
Lymphocytes Increase - (cell/mm^3) (2)	-	>4,000 – 20,000	>20,000
Lymphocytes Decrease - (cell/mm^3) (2)**	<LLN – 800; <LLN – 0.8 x 10^{-9}/L	<800 - 500; <0.8 – 0.5 x 10^{-9}/L	<500 - 200; <0.5 – 0.2 x 10^{-9}/L
Neutrophils Decrease - (cell/mm^3) (2)**	<LLN – 1500; <LLN – 1.5 x 10^{-9}/L	<1500 - 1000; <1.5 – 1.0 x 10^{-9}/L	<1000 - 500; <1.0 – 0.5 x 10^{-9}/L
Eosinophils - (cell/mm^3) (1)	650 – 1500	1501 - 5000	>5000
Platelets Decrease - (cell/mm^3) (2)**	<LLN – 75,000; <LLN – 75.0 x 10^{-9}/L	<75,000 – 50,000; <75.0 – 50.0 x 10^{-9}/L	<50,000 – 25,000; <50.0 – 25.0 x 10^{-9}/L

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

Data Source: (1) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

(2) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

* Those parameters that are not listed do not have grading categories in either the CTCAE or the FDA guidance documents and will therefore be reviewed by the Investigator and only reported as an AE if considered to be clinically relevant.

** Where parameters in this table are listed in both the CTCAE and the FDA guidance documents, and each document has different values within each grading category, the grading in CTCAE guidance document predominates.

ABNORMAL LABORATORY VALUES RATING: URINALYSIS PARAMETERS

Urine*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Protein ** (1)	1+ proteinuria; urinary protein <1.0 g/24 hours	2+ proteinuria; urinary protein 1.0-3.4 g/24 hours	Urinary protein ≥3.5 g/24 hours
Glucose (2)	Trace	1+	2+
Blood – Hematuria ** (1)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self-care ADL

Abbreviations: ADL = Activities of daily living; BUN = Blood urea nitrogen; IV = Intravenous.

Data Source: (1) Common Terminology Criteria for Adverse Events and Common Toxicity Criteria (CTCAE) version 4.03.

(2) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

* Those parameters that are not listed do not have grading categories in either the CTCAE or the FDA guidance documents and will therefore be reviewed by the Investigator and only reported as an AE if considered to be clinically relevant.

** Where parameters in this table are listed in both the CTCAE and the FDA guidance documents, and each document has different values within each grading category, the grading in CTCAE guidance document predominates.