Clinical Study Protocol

ZRHM-REXA-07-JP

Study title:	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting
Short title:	Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting
Registration number:	Not assigned
Study number:	ZRHM-REXA-07-JP
Product name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	Final 3.0
Revision date:	07 April 2014
Authors:	[redacted], PhD, Manager Clinical Science [redacted], MEng MSc, Study Biostatistician [redacted], MD, Medical Safety Officer

SYNOPSIS

Sponsor:

Philip Morris Products S.A.

Name of Product:

Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)

Study Title:

A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting

Study Number:

ZRHM-REXA-07-JP

Short Study Title:

Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting.

Primary Objectives:

The primary objectives of this study are:

- To demonstrate the reduction of primary biomarkers of exposure (BoExp) to harmful and potential harmful constituents (HPHCs) (except Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) (Total NNAL)) in a confinement setting in smokers switching from menthol conventional cigarettes (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and
- To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Secondary Objectives:

The secondary objectives of this study are:

- To evaluate self-reported nicotine/tobacco product use including dual-use in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).
- To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
- To describe the levels of primary and secondary BoExp over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.
- To determine the levels of nicotine over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.
- To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
- To describe the change in Cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.
- To monitor the safety profiles during the study.
- To monitor selected risk markers in a confinement and ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Exploratory Objectives:

The exploratory objectives of this study are:

- To describe the following parameters in a confinement and/or ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:
  - Excretion of mutagenic material in urine.

- Subjective effect of smoking.
- Cytochrome P450 (CYP2A6) activity.
- Nicotine dependence as assessed by the Fagerström test for Nicotine Dependence (FTND) questionnaire.

- To evaluate in smokers switching from mCC to THS 2.2 Menthol and smokers continuing smoking mCC the relationship between nicotine equivalents (NEQ) and:
  - Primary and secondary BoExp .
  - Risk markers.
- To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing smoking mCC:
  - Product evaluation.
  - Smoking pattern.
- To describe the following parameter over the course of the study in smokers switching from mCC to THS 2.2 Menthol:
  - Potential combustion occurrences in tobacco plugs.
  - Filter analysis.
- To describe the product use over the course of the study according to the product preference of the subject.

Study Hypotheses:

The hypothesis to be tested is that the geometric mean level of the BoExp for THS 2.2 Menthol is lower relative to mCC.

For primary BoExp, the hypothesis will be tested on Day 5 for monohydroxylbutenyl-mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA), and carboxyhemoglobin (COHb), and on Day 90 Visit for total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) according to the primary and secondary objectives. For the secondary BoExp, the hypothesis will be tested on Day 5, and if significant, on Day 90.

Study Endpoints:

The primary and secondary BoExp to harmful and potentially harmful constituents (HPHCs) measured in the study are presented below:

Table S1: Biomarkers of Exposure

	Biomarkers of Exposure (BoExp)	HPHCs	Matrix
Primary BoExp on Day 5	monohydroxybutenylmercapturic acid (MHBMA)	1,3-butadiene	Urine
	3-hydroxypropylmercapturic acid (3-HPMA)	acrolein	Urine
	S-phenylmercapturic acid (S-PMA)	benzene	Urine
	carboxyhemoglobin (COHb)	Carbon monoxide (CO)	Blood
Primary BoExp on Day 90 Visit	total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)	4 (methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK)	Urine
Secondary BoExp	carbon monoxide	CO	Exhaled breath
	total 1-hydroxypyrene (total 1-OHP)	pyrene	Urine
	total N-nitrosonornicotine (NNN)	N-nitrosonornicotine	Urine
	4-aminobiphenyl (4-ABP)	4-aminobiphenyl	Urine
	1-aminonaphthalene (1-NA)	1-aminonaphthalene	Urine
	2-aminonaphthalene (2-NA)	2-aminonaphthalene	Urine
	o-toluidine (o-tol)	o-toluidine	Urine
	2-cyanoethylmercapturic acid (CEMA)	acrylonitrile	Urine
	2-hydroxyethylmercapturic acid (HEMA)	ethylene oxide	Urine
	3-hydroxybenzo(a)pyrene	benzo(a)pyrene	Urine
	3-hydroxy-1-methylpropyl-mercapturic acid (HMPMA)	crotonaldehyde	Urine
	S-benzylmercapturic acid (S-BMA)	toluene	Urine
BoExp to nicotine	nicotine equivalents (NEQ) free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide	nicotine	Urine
	Nicotine	nicotine	Plasma
	Cotinine	nicotine	Plasma

Primary Endpoints:

The primary endpoints of this study are:

- To demonstrate the reduction of primary BoExp to HPHCs (except Total NNAL) in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
  - MHBMA, 3-HPMA, S-PMA (concentration adjusted to creatinine) in 24-hour urine,

and COHb in blood (expressed as % of saturation of hemoglobin) as measured on Day 5.

- To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
  - Total NNAL level (concentration adjusted to creatinine) in 24-hour urine as measured on Day 90 Visit.

Evaluation criterion:

The study will be considered successful, if the study demonstrates a 50% reduction or more in MHBMA, 3-HPMA, S-PMA, and COHb at Day 5 and in Total NNAL at Day 90 in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, using a one-sided test with 2.5% type I error probability.

Secondary Endpoints:

The secondary endpoints of this study are:

- To evaluate self-reported nicotine/tobacco product use including dual-use in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).
  - Number of mCC or Menthol Tobacco Sticks smoked daily as reported on the log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.
- To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
  - BoExp listed as secondary (Table S1) (expressed as quantity excreted or concentration adjusted to creatinine) on Day 5 and on Day 90 Visit in 24-hour urine .
- To describe the levels of primary and secondary BoExp over the entire exposure (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.
  - BoExp listed as primary and secondary (Table S1) from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit and Day 90 Visit as follows:
    - CO (expressed as ppm) in exhaled breath

- COHb in blood (expressed as % saturation of hemoglobin)
- Urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

- To determine the levels of nicotine over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.
  - NEQ (expressed as quantity excreted and concentration adjusted to creatinne) (Table S1) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
  - Nicotine and cotinine in plasma from Day 1 to Day 4, Day 5, and on Day 30 Visit, Day 60 Visit, Day 90 Visit.
- To describe the pharmacokinetic profiles of the nicotine and cotinine in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
  - Peak (highest concentration along the day) on Day 5.
  - Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
  - Weighted average concentration over 24 hours on Day 5.
- To describe the change in CYP1A2 enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.
  - Molar metabolic ratio of paraxanthine/caffeine in plasma on Day 5 and Day 90 Visit.
- To monitor the safety profiles during the study.
  - Adverse events (AEs)/serious adverse events (SAEs), and device events including THS 2.2 Menthol malfunction/misuse.
  - Respiratory symptoms: cough assessment by visual analogue scale (VAS) and Likert scales and one open question.
  - Vital signs.
  - Spirometry.
  - Electrocardiogram.
  - Clinical chemistry, hematology, and urine analysis safety panel.
  - Physical examination.

- Concomitant medications.

- To monitor selected risk markers in a confinement and ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.
  - Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit.
  - High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
  - Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
  - Hemoglobin A1c in blood on Day 90 Visit.
  - Soluble inter-cellular adhesion molecule-1 in serum on Day 6, on Day 30, Day 60 and Day 90 Visit.
  - White blood cell and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
  - 8-epi-prostaglandin F2α (8-epi-PGF2α) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24 hour urine on Day 5, Day 30 Visit, Day 60 Visit, Day 90 Visit (expressed as concentration adjusted to creatinine).
  - Body weight and waist circumference on Day 90 Visit.

Exploratory Endpoints

- To describe the following parameters in a confinement and/or ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:
  - Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24 hour urine.
  - Subjective effect of smoking: Questionnaire of Smoking Urges (QSU Brief questionnaire); questionnaire Minnesota Nicotine Withdrawal Scale-Revised on Day 5, and Day 90 Visit.
  - CYP2A6 activity: in plasma on Day 6, and on Day 90 Visit using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.
  - Nicotine dependence as assessed by the FTND questionnaire: score from FTND questionnaire on Day 90 Visit.

- To evaluate in smokers switching from mCC to THS 2.2 Menthol and smokers continuing smoking mCC the relationship between nicotine equivalents (NEQ) and:
  - Primary and secondary BoExp on Day 5 and on Day 90 Visit in 24-hour urine .
  - Selected risk markers (hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, hemoglobin A1c, sICAM-1, white blood cell, platelet count, 8-epi-PGF2α, 11-DTX-B2) in respective body matrix when available, on Day 5 and on Day 90 Visit.
- To describe the following parameters over the course of the study in smokers switching from mCC to the THS 2.2 Menthol as compared to smokers continuing smoking mCC:
  - Product evaluation: Modified Cigarette Evaluation Questionnaire.
  - Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.
- To describe the following parameter over the course of the study in smokers switching from mCC to THS 2.2 Menthol:
  - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
  - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm (during confinement setting only).
- To describe the product use over the course of the study according to the product preference of the subject:
  - Number of mCC or Menthol Tobacco Sticks smoked daily as reported on the log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.

Study Design:

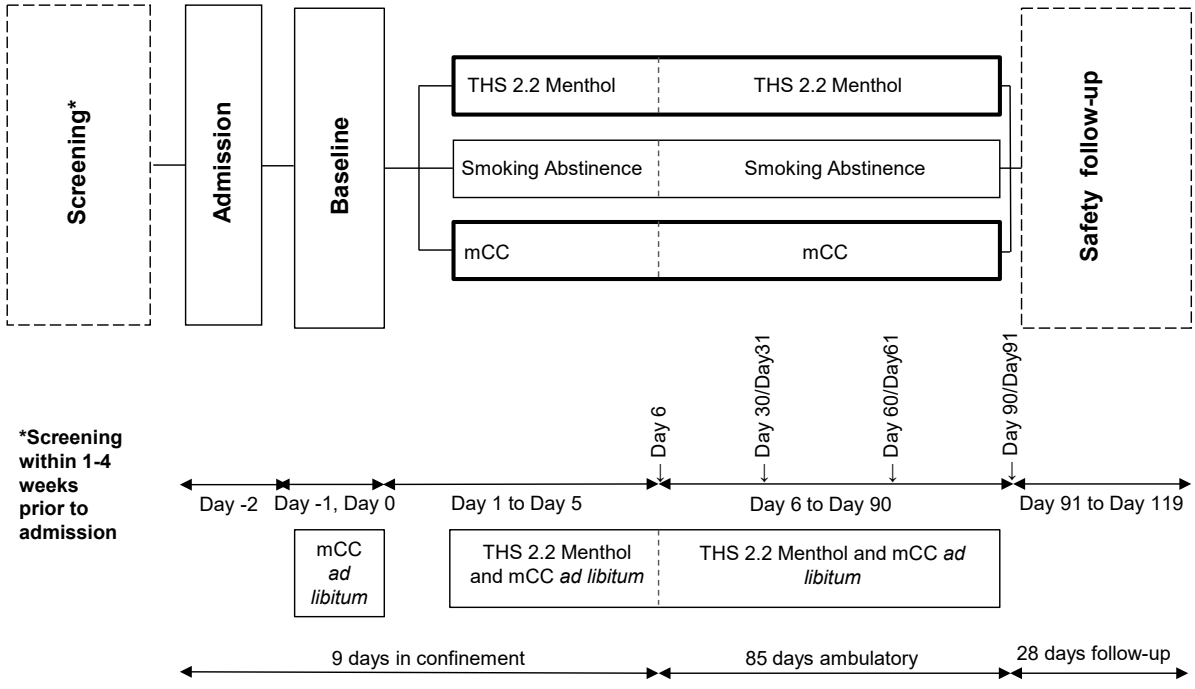
A randomized, controlled, open-label, 3-arm, parallel group study design with a stratified randomization by sex and average daily cigarette consumption over the last 4 weeks as reported during the Screening Visit (smokers smoking 10-19 mCC and smokers smoking >19 mCC per day) (Figure S1).

This is an *ad libitum* smoking study. In general, smoking/product use during the confinement period will be allowed between 06:30 AM and 11:00 PM. During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30

Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from 08:00 AM to 23:00 PM on Day 30, Day 60, and Day 90. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards.

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 Menthol and mCC in THS 2.2 Menthol and mCC arms, respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each Menthol Tobacco Stick/mCC when requested by the subject. During the ambulatory period, the subjects randomized to the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects randomized to the SA arm will be instructed to abstain from smoking.

Figure S1: Study Design



Abbreviations: mCC = Menthol conventional cigarette(s); THS = Tobacco Heating System; Figure not to scale.

- <u>The Screening period covers 4 weeks (Day -30 to Day -3) prior to Admission to the clinic (Day -2):</u>

A demonstration of the THS 2.2 Menthol will be done by the study collaborator during the Screening Visit. Subjects will be in a confined setting for 9 days from Day -2 onwards.

- The run-in period (from Admission on Day -2 until 06:29 AM of Day-1):

Prior to enrolment on Day -2, as the last procedure of the eligibility assessments, subjects will have a product test of the THS 2.2 Menthol (use of up to three THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product test will only be done after pregnancy is excluded by a negative urine pregnancy test. Enrolment takes place after all inclusion and exclusion criteria have been satisfactorily met. Only subjects willing and able to use the product will be enrolled in the study.

- The baseline period (from Day -1, 06:30 AM until Day 1, 06:29 AM):

All subjects will continue smoking their single preferred brand of mCC and baseline values will be recorded. On Day 0, subjects will be randomized to one of the three study arms in a 2:1:1 ratio using a stratified randomization. The full analysis set (FAS) population will be as follows:

- THS 2.2 Menthol Arm: ~80 subjects, *ad libitum* use of the product.
- mCC Arm: ~40 subjects, *ad libitum* use of their preferred mCC brand.
- SA Arm: ~40 subjects who will abstain from smoking.

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

- The exposure period (from Day 1, 06:30 AM until 11:00 PM on Day 90) and Day of Discharge of Day 90 Visit (from 11:00 PM to time of discharge of Day 91):

The exposure period will include both the exposure period in confinement, and the exposure period in ambulatory setting:

- The exposure period in confinement setting (from Day 1, 06:30 AM until time of Discharge on Day 6):

  The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product between 06:30 AM and 11:00 PM in THS 2.2 Menthol and mCC arms. Subjects allocated to the SA arm will be asked to abstain from smoking and will not be provided with medication to support SA. Subjects will be provided with psychological support during the period of smoking abstinence. Use of any tobacco/nicotine containing product other than the assigned product/regimen will not be allowed and may, at the discretion of the Investigator or designee, result in the subject withdrawal from the study.

  Twenty-fourhour urine will be collected from Day -1 to Day 6 on site. The end of the

24-hour urine collection for Day 5 will end in the morning on Day 6 prior to Discharge.

On Day 6, the safety procedures will be conducted before discharge of the subject from the clinic after 9 days in a confined setting. Use of products will be allowed on Day 6 in the THS 2.2 Menthol and mCC arms according to product arm allocation, but only after CYP2A6, cough and MNWS questionnaires and spirometry have been performed.

- The exposure period in ambulatory setting (from time of Discharge on Day 6 until Day 90 11:00 PM) and Day of Discharge of Day 90 Visit (from 11:00 PM to time of discharge of Day 91):

After the time of Discharge on Day 6, subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days. Subjects will be allowed to use nicotine replacement therapy (NRT) if considered necessary by the Investigator or requested by the subject.

Subjects will be required to make three visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each visit will cover 2 consecutive days on site. For Day 30 Visit, the subject will check-in at approximately 08:00 AM on Day 30, and will check-out on Day 31. For Day 60 Visit, the subject will check-in at approximatively 08:00 AM on Day 60, and will check-out on Day 61. For Day 90 Visit, the subject will checked-in at approximately 08:00 AM on Day 90, and will be discharged on Day 91 after having performed all the safety examination procedures.

Twenty four-hour urine will be collected at each ambulatory visit on Day 30 Visit, Day 60 Visit, and Day 90 Visit at the site. The end of the 24-hour urine collection for Day 90 Visit will end in the morning on Day 91 at 09:00 AM.

On Day 30, Day 60, and Day 90, subjects in the THS 2.2 Menthol and mCC arms will be allowed to use their assigned product from approximately 08:00 AM to 23:00 PM. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted. On Day 31, Day 61, product use will be allowed from 06:30 AM. The end of the exposure period will be fixed at Day 90 11:00 PM.

The use of THS 2.2 Menthol will be strictly forbidden for subjects in the mCC or SA arms.

On the day of discharge from Day 90 Visit (from Day 90 11:01 PM until time of discharge of Day 91), subject will be discharged from the investigational site after all safety examination procedures have be conducted.

Subject will not be withdrawn from the study for the use of nicotine/tobacco-containing products other than the assigned product/regimen. Subjects will record in a product use electronic diary any use of CC (menthol or non-menthol), NRT, or other nicotine/tobacco-containing products.

During the confinement and ambulatory settings:

- Subjects in the SA arm will be provided with support including psychological support as requested by the subject or considered necessary by the Investigator or study collaborator.
- During the study, any subjects who want to quit smoking will be encouraged to do so, will be referred to medical services and will be withdrawn from the study. This is applicable for all subjects during screening to the baseline period and for subjects allocated to THS 2.2 Menthol or mCC arms during the exposure period.

- The safety follow-up period (from time of Discharge from Day 91 until Day 119):

After the time of Discharge on the Day 91, subject will enter a 28-day safety follow-up period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found. The end of the study is defined as the time of Discharge on Day 91 plus 28 day follow-up.

Study Population and Main Criteria for Inclusion:

Healthy adult Japanese female or male subjects, meeting the following main inclusion criteria:

- Subject is aged from 23 to 65 years (inclusive).
- Smoking, healthy subject as judged by the Investigator.
- Subject is Japanese.
- Subject smokes at least 10 commercially available mCC per day (no brand restrictions) for the last 4 weeks, based on self-reporting.
- Subject has smoked for at least the last 3 consecutive years.
- Subject does not plan to quit smoking in the next 3 months.
- Subject is ready to accept interruption to smoking for up to 90 days.
- Subject is ready to accept using the THS 2.2 Menthol for up to 90 days.

Subjects who do not complete the study after randomization will not be replaced. However, subjects enrolled at a study site that is discontinued for non-compliance with ICH/GCP will not be included in the primary study populations, and therefore enrolment will be extended to meet the sample size requirement.

Investigational Product; Dose; and Mode of Use

Test Product:

Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)

Reference Product:

The reference product to the THS 2.2 Menthol during the randomized exposure period is the subject's own preferred commercially available single brand of mCC.

Reference Point: SA

Duration of Study:

The entire study duration per subject will be 123 to 150 days, including a Screening period of up to 28 days prior to baseline (Day -30 to Day -3), an 9-day confinement setting (Day -2 to time of Discharge of Day 6) followed by a 85-day ambulatory setting (from the time of Discharge of Day 6 to the time of Discharge on Day 91), and a 28-day safety follow-up period (until Day 119). The end of study is defined as the time of Discharge (Day 91) of the last subject plus 28-day follow-up.

Expected Duration of the Study:

01 July 2013 to 31 August 2014

Sample size:

Approximately, 160 smokers in the full analysis set (FAS) population (~80 in THS 2.2 Menthol arm, ~40 in mCC and ~40 in SA) are required to attain 80% power to show at least a 50% reduction for any of the selected primary BoExps in THS 2.2 Menthol compared to the mCC arm, using a one-sided test with 2.5% type I error probability.

Statistical Methods:

Primary confirmatory endpoint: The hypothesis to be tested is that the geometric mean level

of the BoExp for THS 2.2 Menthol is lower relative to mCC.

For primary BoExp, the hypothesis will be tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and on Day 90 Visit for Total NNAL according to the primary and secondary objectives.

The transformed BoExp data will be analyzed by means of a generalized linear model using product arm as covariate adjusting for the following baseline information: sex, average cigarette consumption over the previous 4 weeks, and baseline value of endpoint. The test will be declared significant if the contrast THS 2.2 Menthol versus mCC is significant. Estimates of differences between groups will be back-transformed to provide relative effects.

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

For BoExp, the geometric mean and coefficient of variation will be presented in addition to the mean and SD.

Analyses over time will be descriptive statistics of parameters at each assessment timepoint.

Unless stated otherwise, all statistical tests will be two-sided and conducted at the 5% level, and all quoted confidence intervals (CI) will be two-sided 95% CI.

The per-protocol (PP) population will be the primary analysis for BoExp, and risk markers. The full analysis set will be the primary analysis set for compliance to randomization arm, exposure and questionnaires. Exposure and questionnaires will be described by randomization arm and according to product use (exclusive THS 2.2 Menthol, dual-use of THS 2.2. Menthol and mCC, mCC exclusive, SA).

A sensitivity analysis will be run on the compliant population for the for BoExp and risk markers.

Safety will be analyzed using the safety population by randomization arm and according to the exclusive THS 2.2 Menthol, dual-use of THS 2.2 Menthol and mCC, mCC exclusive, SA groups.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

11-DTX-B2	11-dehydro-thromboxane B2
1-OHP	1-hydroxypyrene
1-NA	1-aminonaphthalene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
8-epi-PGF2α	8-epi-prostaglandine F2α
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
B	Blood sample required
BMI	Body mass index
BoExp	Biomarker(s) of exposure
BP	Blood pressure
BUN	Blood urea nitrogen
CAF	Caffeine
CC	Conventional cigarette(s)
CD	Compact disc
CEMA	2-cyanoethylmercapturic acid
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
CRA	Clinical Research Associate

CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Event and Common Toxicity Criteria
CTMS	Clinical Trial Management System
CV	Coefficients of variation
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EHCSS	Electrically heated cigarette smoking system
EOS	End of Study
ePRO	Electronic patient report outcome
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GVP	Gas vapor phase
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HEMA	2-hydroxyethyl mercapturic acid
HIV	Human immunodeficiency virus
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHCs	Harmful and potentially harmful constituents
hs-CRP	High-sensitive C-reactive protein
HST	Human smoking topography

IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
IOM	Institute of Medicine
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IU	International unit
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of the normal range
LLOQ	Lower Limit of Quantification
LOCF	Last observation carried forward
mCC	Menthol conventional cigarette
MCEQ	Modified Cigarette Evaluation Questionnaire
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenyl mercapturic acid
MNWS	Minnesota Nicotine Withdrawal Scale (revised version)
MR	Mean ratios
MRTP	Modified risk tobacco product
Neq	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NRT	Nicotine Replacement Therapy

NSAID	Nonsteroidal Anti-inflammatory Drugs
o-tol	o-toluidine
PK	Pharmacokinetic(s)
PMI	Philip Morris International
PP	Per-protocol
PT	Prothrombin time
PX	Paraxanthine
QC	Quality control
QSU	Questionnaire of Smoking Urges (brief version)
RBC	Red blood cell (count)
RNA	Ribonucleic acid
SA	Smoking abstinence
SAE	Serious adverse event
SAP	Statistical analysis plan
S-BMA	S-benzylmercapturic acid
SDTM	Standards Consortium's Study Data Tabulation Model
SES	Socio-economic status
SHM	Sample handling manual
sICAM-1	Soluble inter-cellular adhesion molecule
SOC	System organ class
SOP	Standard Operating Procedure
S-PMA	*S*-phenylmercapturic acid
TC	Total cholesterol
TG	Triglycerides
THS	Tobacco Heating System
TPM	Total particulate matter
U	Urine sample required
UV	Ultra violet
[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

Explanation of Terms

The following special terms are used in this protocol:

Baseline period	06:30 AM at Day -1 until 06:29 AM of Day 1.
Back up subject	Subjects who tested the product and were discontinued from enrollment.
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.
Day 30 Visit, Day 60 Visit, and Day 90 Visit	Day 30 Visit, Day 60 Visit, and Day 90 Visit start on Day 30, Day 60, and Day 90 respectively at approximately 08:00 AM (check-in of the subject on site) until the check-out of the day after respectively on Day 31, Day 61, and the discharge on Day 91. This is to allow 24-hour urine collection.
End of study	End of Study is defined as the time of discharge on Day 91 (Day 90 Visit) of the subject plus 28 days of safety follow-up.
Enrolment	On Day -2 for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily met and the subject is willing and ready to use the THS 2.2 Menthol (the trial of THS 2.2 Menthol is the last assessment prior to enrolment).
Exposure period in confinement	06:30 AM of Day 1 until time of Discharge on Day 6.
Exposure period in the ambulatory setting	From the time of discharge on Day 6 until the time of Discharge on Day 90 11:00 PM.

Investigator	Principal Investigator or sub-investigator
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.
mCC incompatible with HST SODIM® device	All mCCs that are incompatible with the HST SODIM® device (e.g., slim mCC).
Randomization	Assignment of the subject randomization number in the Interactive Web and Voice Response System. This can be done any time on Day 0, however, subjects are **not** to be informed of their randomization group and number prior Day 1.
Run-in period	Admission to site until 06:29 AM of Day -1.
Safety follow-up	After the time of Discharge on the Day 91, a 28-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 g eneral, any AE will be 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 informed consent form (ICF) signature to the time of enrolment will be considered a screening failure and will be replaced by other subjects.
THS Menthol Tobacco Stick	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 Menthol Tobacco Stick)

Time of Discharge	Time of Discharge on Day 6: time when the subject is released from the site (confinement period) after all the procedures of the day of discharge (Day 6) have been conducted prior to entering into the ambulatory period Time of Discharge on Day 91 (Day 90 Visit): time when the subject is released from the site on Day 91 and enters the 28-day safety follow-up period
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: Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable.

1 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

1.1 Institutional Review Board (IRB) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] which includes bothsubject information sheet and informed consent, subject recruitment procedures [e.g. advertisements], written information to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Principal Investigator's curriculum vitae and/or other evidence of qualifications, the list of sub-Investigators and any other documents requested by the Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB. 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 Ministerial Ordinance on Good Clinical Practice for Drugs and local requirements, as applicable.

In accordance with GCP, a written confirmation of the IRB approval should be provided to the Sponsor. This should identify the study (Principal 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 another original copy will be filed in the Study Master File at the Sponsor or designated organization. The study must not start at a study site befo re 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 Principal Investigator or sub-Investigator (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, Ethical Guidelines for Clinical Studies (Ministry of Health, Labour and Welfare, 2003 (as last amended on July 31, 2008)), Ministerial Ordinance on Good Clinical Practice for Drugs (Ministry of Health and Welfare, 1997(as last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 161 of December 28, 2012)), and applicable regulatory principles.The Principal Investigator agree to conduct the clinical study in compliance with the protocol agreed upon 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 Study consent/Subject Information Sheet for Study Participation

Before or at the Screening Visit, the Investigator or designee 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 by the date and signature of both the subject and the person who conducted the inform consent discussion. No study-specific procedures will be performed before the ICF has been signed.

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

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.

1.3.2 Informed Consent Form/Subject Information Sheet for Long-term Bio-Banking

In addition to the ICF for the participation in the study, each subject will be asked for consent to the additional bio-banking for measurements of BoExp and risk markers in serum/plasma and urine and for consent to the additional bio-banking of blood for further transcriptomics (pharmacogenomics) analysis.

1.3.2.1 Bio-bank for Biomarkers of Exposure and Risk Markers

There will be a separate subject information and consent for samples (serum/plasma/urine) that will be stored in a bio-bank for subsequent analysis of biomarkers of exposure (BoExp) and/or risk markers following completion of this study. No genetic or transcriptomics testing will be done on these samples.

1.3.2.2 Bio-bank for Transcriptomics

Subjects will be provided with information and asked for their consent to collect blood samples for bio-banking for transcriptomics (pharmacogenomics) in order to study the variation of the ribonucleic acid (mRNA and miRNA) in smokers using THS 2.2 Menthol as compared to smokers continuing to smoke mCC or smokers switching to smoking abstinence. Comparison will be based on previously described biological networks. In-house data from an exploratory study to assess the reduction of exposure to HPHCs (clinical trial dot. gov identifier: NCT01780714) in smokers switching to THS 2.1 as compared to smokers continuing smoking CC shows that using THS 2.1, the earlier version of THS 2.2 results in significant variation of RNA characteristics as compared to smoking CC.

1.3.2.3 Information on Optional Consent to Bio-banking

Each subject will be given full and adequate oral and written information about the nature, purpose, possible risks and benefits of bio-banking, and the Investigator will answer all questions the subject might have to his/her full satisfaction. The subject 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 by the date and signature of both the subject and the Investigator and personnel who conducted the informed consent discussion. The subject's consent to storage of any samples in a bio-bank or for transcriptomics is not a requirement for study participation and the subject's participation in the study does not depend on their providing consent for sample bio-banking.

1.3.3 Amendment to the Informed Consent Form/Subject Information Sheet.

If a protocol amendment is required, or if new information regarding the risk profile of the Investigational Product (IP) becomes available, an amendment may be required to the ICF. If revision of the ICF is necessary, the Principal 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.

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 the 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 or designee will carry out the clinical study in accordance with ICH GCP Ethical Guidelines for Clinical Studies.

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). The effects of smoking and smoking cessation on mortality from cardiovascular disease among the Japanese population were investigated in cohort studies in Japan. These studies confirmed the association between smoking and mortality from cardiovascular disease and highlighted the importance of smoking cessation at any age to prevent cardiovascular disease in the Japanese population (Honjo et al., 2010a, Iso et al., 2005). In 2000 in Japan, the proportion of adult deaths due to smoking ranges from 20.0% to 24.9% in males and from 10.0% to 14.6% in females. In 2007, Japan became part of the top five conventional cigarette (CC)-consuming countries with a consumption of 234 billion annualy in 2009 (tobacco atlas, fourth edition). 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 can't 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 US 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 that are acceptable to smokers as substitutes for CCs. PMI is developing MRTPs that provide a smoking experience without combustion. The novel approach to achieve this is by heating tobacco at significantly lower temperatures than required 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 (IOM) 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, and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs). 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 mCC. PMI believe 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 mCC.

The product developed by PMI, and to be assessed in this study, is the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for CC, which can reach 900°C. The THS 2.2 Menthol is composed of the 'THS Tobacco Stick Holder', dedicated special Menthol Tobacco Sticks made of conventional tobacco, a charger, and different accessories. The energy of the THS Tobacco Stick Holder is sufficient to maintain approximately a 6 minutes session. Unlike CC, 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 described in the investigator's brochure (PMI, 2013a) supports the initiation of the clinical studies. 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) (www.clinical trial.gov identifier: NCT01780688) and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1 (www.clinical trial. gov identifier: NCT01780714). 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 overall goal of the study is to provide information on the reduction in the levels of selected BoExp to HPHCs and to obtain safety information in subjects using the THS 2.2 Menthol as compared to smokers continuing smoking their preferred brand of mCC in confinement setting for 5 days followed by an ambulatory setting of 85 days. Smokers who will be asked to abstain from using any nicotine/tobacco-containing products will be used as a reference point. The smokers allocated to the THS 2.2 Menthol and mCC arms will be allowed to use the product they are allocated to ad libitum.

Additional purpose of the study aim is to understand the effect of using THS 2.2 Menthol on selected variables and their potential association to the reduced exposure to HPHCs (e.g. additional BoExp, cytochrome P450 1A2 (CYP1A2) and cytochrome P450 2A6 (CYP2A6) enzymatic activity, pharmacokinetic (PK) profile of nicotine and cotinine, product evaluation, product use and related subjective effects, human smoking topography, risk markers).

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

In Japan, research conducted by the Ministry of Health, Labour and Welfare has shown that 35.9% of male and 43.6% of female respondents over 20 years of age expressed the wish to quit smoking (International Tobacco Online, 2012). In a large follow-up study of middle aged Japanese smokers, the predictors of smoking cessation were age, job, smoking habit, physical activity, health checkup participation, and health status (Honjo et al., 2010b). Advice on health risks associated with smoking and smoking cessation advice will be provided at Screening, at Admission, on Day 6 and on Day 90 Visit. The advice will follow the recommendations of the World Health Organization (WHO) (Raw et al., 2002) -"Evidence based Recommendations on the Treatment of Tobacco Dependence". 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.
- 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/mCC)

- Change in smoking habits due to study requirements and related concomitant symptoms, (e.g., craving, withdrawal symptoms).
- All risks related to study procedures, IP, 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 local blood donation standards).
- Management and follow-up of adverse events (AEs)/serious adverse events (SAEs).

2.3.4 Unforeseeable Risks

As with any new IP, there may be unforeseeable risks and hazards that could occur. The possibility of such will be explained at Screening and at Admission. 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 objectives of this study are:

- To demonstrate the reduction of primary biomarkers of exposure (BoExp) to HPHCs (except Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) (Total NNAL) in a confinement setting in smokers switching from menthol conventional cigarettes (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and
- To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate self-reported nicotine/tobacco product use including dual-use in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).
- To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
- To describe the levels of primary and secondary BoExp over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.
- To determine the levels of nicotine over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.
- To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
- To describe the change in Cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.
- To monitor the safety profiles during the study.

- To monitor selected risk markers in a confinement and ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To describe the following parameters in a confinement and/or ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:
  - Excretion of mutagenic material in urine.
  - Subjective effect of smoking.
  - Cytochrome P450 (CYP2A6) activity.
  - Nicotine dependence as assessed by the Fagerström test for Nicotine Dependence (FTND) questionnaire.
- To evaluate in smokers switching from mCC to THS 2.2 Menthol and smokers continuing smoking mCC the relationship between nicotine equivalent (NEQ) and:
  - Primary and secondary BoExp.
  - Risk markers.
- To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing smoking mCC:
  - Product evaluation.
  - Smoking pattern.
- To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol:
  - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
  - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm (during confinement setting only).
- To describe the product use over the course of the study according to the product preference of the subject.

3.4 Study Endpoints

The primary and secondary BoExp to harmful and potentially harmful constituents (HPHCs) measured in the study are presented in Table 1:

Table 1. Biomarkers of Exposure

	Biomarkers of Exposure (BoExp)	HPHCs	Matrix
Primary BoExp on Day 5	monohydroxybutenylmercapturic acid (MHBMA)	1,3-butadiene	Urine
	3-hydroxypropylmercapturic acid (3-HPMA)	acrolein	Urine
	S-phenylmercapturic acid (S-PMA)	benzene	Urine
	carboxyhemoglobin (COHb)	Carbon monoxide (CO)	Blood
Primary BoExp on Day 90 Visit	total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)	4 (methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK)	Urine
Secondary BoExp	carbon monoxide	CO	Exhaled breath
	total 1-hydroxypyrene (total 1-OHP)	pyrene	Urine
	total N-nitrosonornicotine (NNN)	N-nitrosonornicotine	Urine
	4-aminobiphenyl (4-ABP)	4-aminobiphenyl	Urine
	1-aminonaphthalene (1-NA)	1-aminonaphthalene	Urine
	2-aminonaphthalene (2-NA)	2-aminonaphthalene	Urine
	o-toluidine (o-tol)	o-toluidine	Urine
	2-cyanoethylmercapturic acid (CEMA)	acrylonitrile	Urine
	2-hydroxyethylmercapturic acid (HEMA)	ethylene oxide	Urine
	3-hydroxybenzo(a)pyrene	benzo(a)pyrene	Urine
	3-hydroxy-1-methylpropyl-mercapturic acid (HMPMA)	crotonaldehyde	Urine
	S-benzylmercapturic acid (S-BMA)	toluene	Urine
BoExp to nicotine	nicotine equivalents (NEQ) free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide	nicotine	Urine
	Nicotine	nicotine	Plasma
	Cotinine	nicotine	Plasma

3.4.1 Primary Endpoints

- To demonstrate the reduction of primary BoExp to HPHCs (except Total NNAL) in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
    - MHBMA, 3-HPMA, S-PMA (concentration adjusted to creatinine) in 24-hour urine, and COHb in blood (expressed as % of saturation of hemoglobin) as measured on Day 5.
- To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
    - Total NNAL level (concentration adjusted to creatinine) in 24-hour urine fraction as measured on Day 90 Visit.

Evaluation criterion:

The study will be considered successful, if the study demonstrates a 50% reduction or more in MHBMA, 3-HPMA, S-PMA, and COHb at Day 5 and in Total NNAL at Day 90 in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, using a one-sided test with 2.5% type I error probability.

3.4.2 Secondary Endpoints

- To evaluate self-reported nicotine/tobacco product use including dual-use in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).
    - Number of mCC or Menthol Tobacco Sticks smoked daily as reported on the log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.
- To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
    - BoExp listed as secondary (expressed as quantity excreted or concentration adjusted to creatinine) (Table 1) as measured in 24-hour urine on Day 5 and on Day 90 Visit .
- To describe the levels of primary and secondary BoExp over the entire exposure (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.

- BoExp listed as primary and secondary (Table 1) from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit and Day 90 Visit as follows:
  - CO (expressed as ppm) in exhaled breath
  - COHb in blood (expressed as % saturation of hemoglobin)
  - Urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine

- To determine the levels of nicotine over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.
  - NEQ (expressed as quantity excreted and concentration adjusted to creatinne) (Table 1) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit .
  - Nicotine and cotinine in plasma from Day 1 to Day 4, Day 5, and on Day 30 Visit, Day 60 Visit, Day 90 Visit.
- To describe the pharmacokinetic profiles of the nicotine and cotinine in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.
  - Peak (highest concentration along the day) on Day 5.
  - Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
  - Weighted average concentration over 24 hours on Day 5.
- To describe the change in CYP1A2 enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.
  - Molar metabolic ratio of paraxanthine/caffeine in plasma on Day 5 and Day 90 Visit.

- To monitor the safety profiles during the study.
  - Adverse events (AEs)/serious adverse events (SAEs), and device events including THS 2.2 Menthol malfunction/misuse.
  - Respiratory symptoms: cough assessment by visual analogue scale (VAS) and Likert scales and one open question.

- Vital signs.
- Spirometry.
- Electrocardiogram.
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medications.

- To monitor selected risk markers in a confinement and ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.
  - Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit.
  - High sensitive C-reactive protein (hs-CRP) , homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC) in serum on Day 30 Visit, Day 60 visit, and Day 90 Visit.
  - Fibrinogen in plasma on Day 30 Visit, Day 60 visit, and Day 90 Visit
  - Hemoglobin A1c in blood on Day 90 Visit.
  - Soluble inter-cellular adhesion molecule-1 in serum on Day 6, on Day 30 Visit, Day 60 Visit and Day 90 Visit.
  - White blood cell (WBC) and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
  - 8-epi-prostaglandin F2α (8-epi-PGF2α) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24 hour urine on Day 5 Day 30 Visit, Day 60 Visit and Day 90 Visit (expressed as concentration adjusted to creatinine).
  - Body weight and waist circumference on Day 90 Visit.

3.4.3 Exploratory Endpoints

- To describe the following parameters in a confinement and/or ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:
  - Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24 hour urine.

- Subjective effect of smoking: Questionnaire of Smoking Urges (QSU Brief questionnaire); questionnaire Minnesota Nicotine Withdrawal Scale-Revised on Day 5, and Day 90 Visit.
- CYP2A6 activity: in plasma on Day 6, and on Day 90 Visit using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.
- Nicotine dependence as assessed by the FTND questionnaire: score from FTND questionnaire on Day 90 Visit.

- To evaluate in smokers switching from mCC to THS 2.2 Menthol and smokers continuing smoking mCC the relationship between nicotine equivalent (NEQ) and:
  - Primary and secondary BoExp on Day 5 and on Day 90 Visit in 24-hour urine .
  - Selected risk markers (hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, hemoglobin A1c, sICAM-1, white blood cell, platelet count, 8-epi-PGF2α, 11-DTX-B2) in respective body matrix when available on Day 5 and on Day 90 Visit.
- To describe the following parameters over the course of the study in smokers switching from mCC to the THS 2.2 Menthol as compared to smokers continuing smoking mCC:
  - Product evaluation: Modified Cigarette Evaluation Questionnaire.
  - Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.
- To describe the following parameter over the course of the study in smokers switching from mCC to THS 2.2 Menthol:
  - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
  - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm (during confinement setting only).
- To describe the product use over the course of the study according to the product preference of the subject:
  - Number of mCC or Menthol Tobacco Sticks smoked daily as reported on the log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.

4 INVESTIGATIONAL PLAN

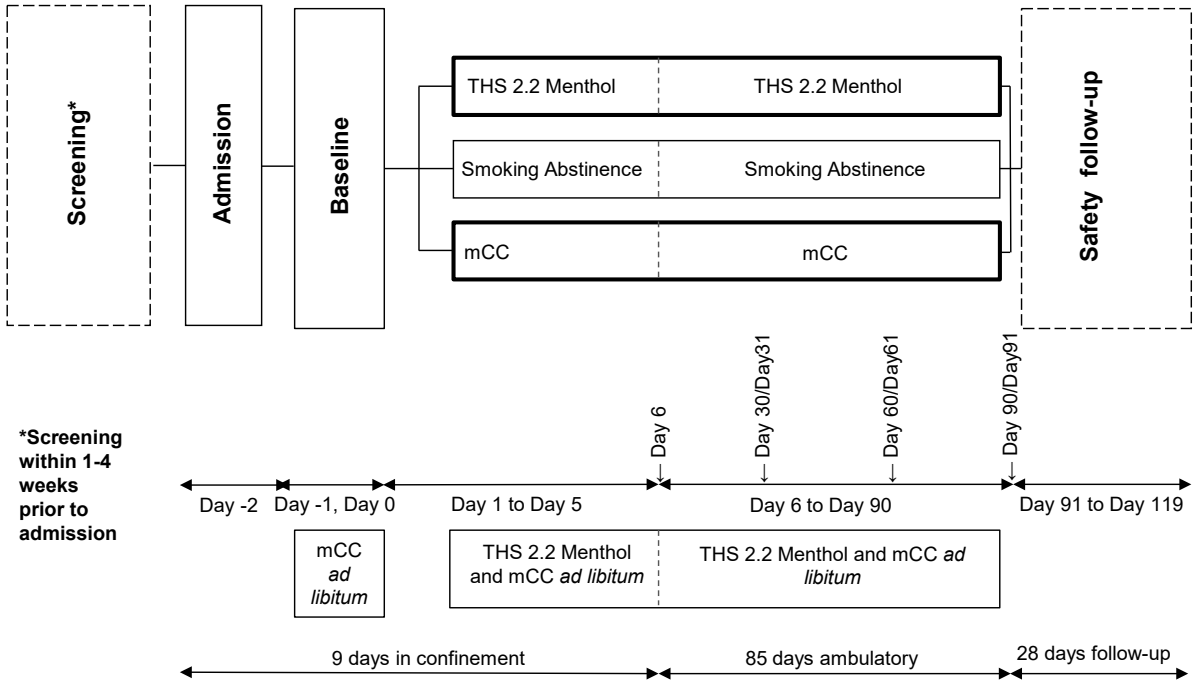
4.1 Overall Study Design and Plan

A randomized, controlled, open-label, 3-arm, parallel group study design with a stratified randomization by sex and daily average cigarette consumption over the last 4 weeks as reported during the Screening Visit (smokers smoking 10-19 mCC and smokers smoking >19 mCC per day) (Figure 1).

This is an *ad libitum* smoking study. In general, smoking/product use during the confinement period will be allowed between 06:30 AM and 11:00 PM. During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from 08:00 AM to 23:00 PM on Day 30, Day 60, and Day 90. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted.On Day 31, Day 61, product use will be allowed from 06:30 AM onwards.

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 Menthol and mCC in THS 2.2 Menthol and mCC arms, respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each Tobacco Stick/mCC when requested by the subject. During the ambulatory period, the subjects randomized to the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects randomized to the SA arm will be instructed to abstain from smoking.

Figure 1. Study design



Abbreviations: mCC = Menthol conventional cigarette(s); THS = Tobacco Heating System; Figure not to scale.

- <u>The Screening period covers 4 weeks (Day -30 to Day -3) prior to Admission to the clinic (Day -2):</u>

  A demonstration of the THS 2.2 Menthol will be done by the study collaborator during the Screening Visit. Subjects will be in a confined setting for 9 days from Day -2 onwards.

- <u>The run-in period (from Admission on Day -2 until 06:29 AM of Day-1):</u>

  Prior to enrolment on Day -2, as the last procedure of the eligibility assessments, subjects will have a product test of the THS 2.2 Menthol (use of up to three THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product test will only be done after pregnancy is excluded by a negative urine pregnancy test. Enrolment takes place after all inclusion and exclusion criteria have been satisfactorily met. Only subjects willing and able to use the product will be enrolled in the study.

- <u>The baseline period (from Day -1, 06:30 AM until Day 1, 06:29 AM):</u>

All subjects will continue smoking their single preferred brand of mCC and baseline values will be recorded. On Day 0, subjects will be randomized to one of the three study arms in a 2:1:1 ratio using a stratified randomization. The FAS population will be as follows:

- THS 2.2 Menthol Arm: ~80 subjects, ad libitum use of the product.
- mCC Arm: ~40 subjects, ad libitum use of their preferred mCC brand.
- SA Arm: ~40 subjects who will abstain from smoking.

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

- The exposure period (from Day 1, 06:30 AM until 11:00 PM onDay 90) and Day of Discharge of Day 90 Visit (from 11:00 PM to time of discharge of Day 91):

The exposure period will include both the exposure period in confinement, and the exposure period in ambulatory setting:

- The exposure period in confinement setting (from Day 1, 06:30 AM until time of Discharge on Day 6):

  The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product between 06:30 AM and 11:00 PM in THS 2.2 Menthol and mCC arms. Subjects allocated to the SA arm will be asked to abstain from smoking and will not be provided with medication to support SA. Subjects will be provided with psychological support during the period of smoking abstinence. Use of any tobacco/nicotine containing product other than the assigned product/regimen will not be allowed and may, at the discretion of the Investigator, result in the subject withdrawal from the study.

  Twentyfour-hour urine will be collected from Day -1 to Day 5 on site. The end of the 24-hour urine collection for Day 5 will end in the morning on Day 6 prior to Discharge.

  On Day 6, the safety procedures will be conducted before discharge of the subject from the clinic after 9 days in a confined setting. Use of products will be allowed on Day 6 in the THS 2.2 Menthol and mCC arms according to product arm allocation, but only after CYP2A6, cough and MNWS questionnaires and spirometry have been performed.

- Exposure period in ambulatory setting (from time of Discharge on Day 6 until Day 90 11:00 PM) and Day of Discharge (from Day 90 11:01 PM until time of discharge of Day 91:

After the time of Discharge on Day 6, subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days. Subjects will be allowed to use nicotine replacement therapy (NRT) if considered necessary by the Investigator or requested by the subject.

Subjects will be required to make three visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each visit will cover 2 consecutive days on site. For Day 30 Visit, the subject will check-in at approximatively 08:00 AM on Day 30, and will check-out on Day 31. For Day 60 Visit, the subject will check-in at approximatively 08:00 AM on Day 60, and will check-out on Day 61. For Day 90 Visit, the subject will checked-in at approximatively 08:00 AM on Day 90, and will be discharged on Day 91 after having performed all the safety examination procedures.

Twenty four-hour urine will be collected at each ambulatory visit on Day 30 Visit, Day 60 Visit, and Day 90 Visit at the site. The end of the 24-hour urine collection for Day 90 Visit will end in the morning on Day 91 at 09:00 AM.

On Day 30, Day 60, and Day 90, subjects in the THS 2.2 Menthol and mCC arms will be allowed to use their assigned product from approximately 08:00 AM to 23:00 PM. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted.On Day 31, Day 61, product use will be allowed from 06:30 AM. The end of the exposure period will be fixed at Day 90 11:00 PM.

The use of THS 2.2 Menthol will be strictly forbidden for subjects in the mCC or SA arms.

On the day of discharge from Day 90 Visit (from Day 90 11:01 PM until time of discharge of Day 91), subject will be discharged from the investigational site after all safety examination procedures have be conducted.

Subject will not be withdrawn from the study for the use of nicotine/tobacco-containing products other than the assigned product/regimen. Subjects will record in a product use electronic diary any use of CC (menthol or non-menthol), NRT, or other nicotine/tobacco-containing products.

During the confinement and ambulatory settings:

Subjects in the SA arm will be provided with support including psychological support as requested by the subject or considered necessary by the Investigator/study collaborator.

During the study, any subjects who want to quit smoking will be encouraged to do so, will be referred to medical services and will be withdrawn from the study. This is applicable for all

subjects during screening to the baseline period and for subjects allocated to THS 2.2 Menthol or mCC arms during the exposure period.

- The safety follow-up period (from time of Discharge from Day 91 until Day 119):

After the time of Discharge on the Day 91, subject will enter a 28-day safety follow-up period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found. The end of the study is defined as the time of Discharge on Day 91 plus 28 day follow-up.

4.2 Rationale for Study Design and Control Groups

The minimum age of 23 years age in the inclusion criteria was selected based on:

- The legal age of smoking in Japan is 20 years.
- To account for the 3 years of smoking history.

This clinical study aims to demonstrate reductions in exposure to selected HPHCs in smokers switching to the THS 2.2 Menthol, a candidate MRTP, as compared to using mCCs (see current version of the IB). The main reference in this study will be smokers who continue to smoke mCC. Smokers who stop smoking (the SA arm) will be used as a reference point for the maximum possible reduction in exposure to HPHCs.

In this study, smokers of mCC will be assessed because the menthol brands play a significant role within the Japanese market, with 20% of the overall market share in 2008 (Connolly et al., 2011).

The confinement period will provide information on maximum possible exposure reductions in a well-controlled environment and will allow full control of daily cigarette consumption. The ambulatory period will provide a perspective of product usage in the real world setting, where smoking of a few CC (menthol and non-menthol) in addition to THS 2.2 Menthol and SA is expected. It will provide information on reduction in selected BoExp and related changes in selected risk markers when THS 2.2 Menthol is used in a real world setting.

The choice of HPHCs to be assessed in this study is derived from the World Health Organization (WHO) (Ashley et al., 2008) and the draft guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke (FDA, 2011).

In the WHO list, 9 HPHCs (acrolein, CO, 1-3 butadiene, benzene, NNN, NNK, acetaldehyde, benzo[a]pyrene, and formaldehyde) with evidence of carcinogenicity, respiratory and cardiac toxicity were recommended to be measured as priority in the smoke chemistry for mandated

lowering (Ashley et al., 2008). Exposure to 4 HPHCs (acrolein, CO, 1,3-butadiene, and benzene) among these nine priority HPHCs will be assessed by measuring their respective BoExp as primary endpoints after 5 days of exclusive use of THS 2.2 Menthol, mCC or SA. The following characteristics apply to these primary BoExp:

- They are several-fold higher in smokers than in smokers abstinent from smoking (Lindner et al., 2011).
- They exhibit, on average, an elimination half-life of ≤24 hours. Therefore, the 5 days of exposure are sufficient to reach the steady state with the THS 2.2 Menthol and SA arms (4 to 5 times the half-life will lead to less than 5% of the original exposure levels of assessed biomarkers on Day 5).
- They were decreased in smokers who switched to another candidate MRTP tested in exploratory studies for 5 days, similar to that observed in smokers who stopped smoking (data on file from the previous study, YVD-CS01-EU study).

Total NNAL was selected as primary endpoints after 90 days of THS 2.2 Menthol use as:

- This biomarker is tobacco specific (Goniewicz et al., 2009), and exhibits, on average, an elimination half-life of 10 to 15 days. Therefore, the 90 days of exposure are sufficient to reach the steady state with the THS 2.2 Menthol and SA arms (4 to 5 times the half-life will lead to less than 5% of the original exposure levels on Day 90 Visit).
- It was decreased in smokers who switched to another candidate MRTP after 5 days, (data on file from the previous study, YVD-CS01-EU study).

In addition, some risk markers have been selected in order to evaluate biological changes in THS 2.2 Menthol arm as compared to mCC arm using SA arm as a reference point to verify if the trend of changes upon THS 2.2 Menthol use follow the same trajectory as SA. Among the ones selected, some well-known to be affected by smoking and to be reversible upon SA, will be measured in this study as follows:

1. CYP1A2 activity, the enzyme which mainly metabolizes nicotine, is decreased as soon as 5 days of smoking abstinence and after 5 days of use of another candidate MRTP (Faber et al., 2004) and data on file from a previous study [YVD-CS01-EU study]).
2. Platelet function will be assessed by measuring 11-DTX-B2 (a major stable metabolite of thromboxane A2, which elicits mainly platelet aggregation). This marker was decreased after 1 week of SA (Benowitz et al., 1993) and after 5 days of use of another candidate MRTP (YVD-CS01-EU study).

3. Blood pressure, hs-CRP, fibrinogen, homocysteine, fasting blood glucose, LDL, HDL, triglycerides, total cholesterol, HbA1c, waist circumference, sICAM-1, WBC, and 8-epi-PGF2α will be evaluated as additional risk markers (Eliasson et al., 2001; Vasan, 2006) for cardiovascular monitoring purposes. According to the literature, some of these risk markers are known to be sensitive to smoking cessation: the levels of HDL increase when the levels of sICAM-1, WBC, and 8-epi-PGF2α decrease following 1 to 3 months of smoking cessation (Pilz et al, 2000; Eliasson et al., 2001).
4. Body weight as a mean increase of 4.5 kg in body weight is observed after 12 months of smoking abstinence with the most weight gain occurring within the first 3 months of quitting (Aubin et al., 2012).

In addition, CYP2A6 activity, the enzyme involved in nicotine metabolism will be assessed in this study to evaluate if the use of THS 2.2 Menthol impacts the activity of this enzyme.

Other parameters such as human smoking topography, product evaluation, and subjective effects including smoking urges and withdrawal symptoms will be evaluated.

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, educational and socio-economic status, tobacco use history, expectations of the effects of the products tested, nicotine exposure, health and mental health status and use of psychoactive substances. In order to capture, these data, subjects will be aked questions about their socio-economic status on Day 4. Such data would allow to compare populations across studies.

All subjects will be asked to provide their own mCC according to their anticipated needs for the whole confinement period. This is to minimize any changes in their smoking behavior due to the participation in the study.

4.3 Appropriateness of Measurements

The laboratory measures to be utilized in this study were selected based on the following criteria: 1) the availability of a validated analytical method, and 2) measure is known to be directly or indirectly affected by smoking; 3) measure is readily reversible after smoking cessation, 4) timeframe of reversibility of measure in the perspective of the study duration, 5) practicality/acceptability by subjects, and 6) robustness (rapid, simple, accurate).

All questionnaires utilized for this study, except the cough, the socio-economic questionnaire, risk/perception and intent to use questionnaire and HST questionnaires, are available as validated questionnaires.

4.4 Study Duration

The entire study duration per subject will be 123 to 150 days, including a Screening period of up to 28 days prior to baseline (Day -30 to Day -3), a 9-day confinement setting (Day -2 to time of Discharge of Day 6) followed by a 85-day ambulatory setting (from the time of Discharge of Day 6 to the time of Discharge on Day 91), and a 28-day safety follow-up period (until Day 119). The end of study is defined as the time of Discharge on Day 91) of the last subject plus 28-day follow-up.

5 STUDY POPULATION

5.1 Selection of Study Population

Healthy, adult Japanese subjects who smoke at least 10 mCC per day for the last 4 weeks with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) per cigarette will be included in this study. Enough subjects will be enrolled into the study until there are 160 smokers in the FAS population.

The maximum number of mCC smoked per day is not limited. Subjects will have a smoking history of at least 3 years of consecutive smoking prior to the Screening Visit. There will be no brand restrictions as long as the cigarettes are flavored with menthol. 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. The smoking status will be verified with a urinary cotinine test (cotinine ≥ 200 ng/mL). Each sex and each of the smoking strata (those smoking 10 to 19 mCC and those smoking > 19 mCC per day as reported by the subject in the 4 weeks prior to the Screening Visit) should have a quota applied to ensure they represent at least 40% of the population.

5.1.1 Inclusion Criteria

At the Screening Visit/day of Admission, each subject must meet the following criteria:

Inclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
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 23 to 65 years (inclusive).	Safety	X	
3. Subject is Japanese.	Effect	X	
4. Smoking, healthy subject as judged by the Investigator based on all available assessments from the Screening period/day of Admission (e.g. safety laboratory,	Safety	X	X

Inclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
spirometry [FEV_1/FVC >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV_1 >80% predicted value, and post-bronchodilator FVC >80% predicted value], vital signs, physical examination, ECG, chest X-ray and medical history).			
5. Subject smokes at least 10 commercially available menthol mCCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/mCC, as labelled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject has been smoking for at least the last three consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine ≥200 ng/mL).	Effect	X	X
6. The subject does not plan to quit smoking in the next 3 months.	Safety	X	
7. The subject is ready to accept interruptions of smoking for up to 90 days.	Safety	X	X
8. The subject is ready to accept using the THS 2.2 Menthol.	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 -2)
1. As per Investigator judgment, the subject cannot participate in the study for any reason (e.g. medical, psychiatric and/or social reason).	Safety	X	X
2. A subject who is legally incompetent, physically or mentally incapable of giving consent (e.g. emergency situation, under guardianship, 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 ≥32 kg/m2.	Safety	X	
5. As per Investigator judgment, the subject has medical conditions	Effect	X	X

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
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.			
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 five half-lives of the drug (whichever is longer) prior to the Admission Day (Day -2), which has an impact on CYP1A2 or CYP2A6 activity.	Effect		X
8. If a subject has received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -2), it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives or subject's safety.	Effect	X	X
9. Concomitant use of NSAIDs or acetylsalicylic acid.	Effect	X	X

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
10. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in the study.	Administrative	X	X
11. The subject has a positive urine drug test.	Administrative	X	X
12. Positive serology test for HIV1/2, hepatitis B or hepatitis C.	Safety	X	
13. Donation or receipt of whole blood or blood products within 3 months prior to Admission.	Safety	X	X
14. The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).	Administrative	X	
15. 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	
16. The subject has participated in a clinical study within 3 months prior to the Screening Visit.	Safety	X	
17. 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	
18. For women only: Subject is pregnant (does not have negative pregnancy tests at Screening	Safety	X	X

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
and at Admission) or is breast feeding.			
19. For women only: Subject does not agree to use an acceptable method of effective contraception*	Safety	X	X

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

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 the Source Document and electronic Case Report Form (eCRF).

When a subject withdraws or is removed from the study, the whole safety examination procedure planned on Day 6 must be performed as soon as possible after the time of withdrawal unless the subject has withdrawn their informed consent to do so. After the time of withdrawal, the subject will enter into the 28-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 (any invasive procedures, including the drawing of blood MUST NOT be performed after diagnosis of pregnancy, see Section 8.5.
- The Sponsor or Principal Investigator terminates the study. If the Sponsor or the Principal Investigator decide to prematurely terminate the study, the subject will be promptly informed and will follow the end of study procedures as described in Section 9.5. The head of the medical institution will report this fact and the reason in writing to the IRB. If a study site is discontinued for non-compliance with ICH/GCP, subjects enrolled at that

site will not be included in the primary study populations, and therefore enrolment will be extended to meet the sample size requirement.

- Withdrawal is considered to be in the best interest of the subject or the other subjects.
- The subject wish to quit smoking (this is applicable for all subjects during screening to the baseline period and for subjects allocated to THS 2.2 Menthol or mCC arms during the exposure period).

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 CRO Medical Monitor on an ongoing basis).
- If a subject uses any CC or nicotine/tobacco-containing product other than the product/regimen he/she is assigned to, it will be at the discretion of the Investigator to decide whether or not to withdraw the subject from the study.
- Non-compliance to the study procedures.

Smoking of CC (menthol and non-menthol) in the THS 2.2 Menthol or SA arms during the ambulatory period will not be considered a reason for withdrawal of the subject from the study. However, the smoking of CCs (menthol and non-menthol) or use of any nicotine/tobacco-containing products including NRT other than the product/regimen the subject is assigned to during the ambulatory period will be documented in the daily product use electronic diary. Subjects withdrawn prematurely after randomization will not be replaced and will not be allowed to re-enter the study. All subject withdrawals have to be documented properly in the source documentation and 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 (Day -2) will be considered a screening failure until the time of enrolment and will be replaced by other subjects.

Subjects who violate the entry criteria prior to enrolment, but who are considered eligible, will be immediately withdrawn from the study when the violation is detected. If subjects are not yet randomized, they can be replaced.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

6.1.1 Test Product

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.
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)
THS Menthol Tobacco Stick (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.

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 mCC.

The THS 2.2 Menthol will be provided by the Sponsor.

Per cigarette/Tobacco Stick tar, nicotine, and carbon monoxide yields are measured by standardized machined 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, 2012a; PMI, 2012b; PMI, 2013b). Another method is the more intensive smoking method developed by Health Canada (Health Canada, 1999).

Table 2 below lists the commonly reported measures (PMI, 2013a):

Table 2. Measured Aerosol Fractions for the THS Menthol Tobacco Sticks

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

NFDPM: Nicotine-free dry particulate matter

[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).

6.1.2 Reference Product / Baseline Period Products

During the run-in period (Admission to clinic until 06:29 AM of Day -1) and the baseline period (from 06:30 AM of Day -1 until 06:29 AM of Day 1), all subjects will continue smoking their preferred commercially available single brand of mCC. Subjects are not allowed to roll their own mCC.

The reference product to the THS 2.2 Menthol during the randomized exposure period is the subject's own preferred commercially available single brand of mCC.

All eligible subjects will be asked to purchase their own preferred single brand of mCC prior to Admission and provide his/her anticipated amount of mCC for a total of 9 days plus 4 extra packs on Day -2 (Admission Day) to the site study collaborator. The mCCs will not be provided by the Sponsor.

During the ambulatory period, for the Day 30 Visit, Day 60 Visit, and Day 90 Visit, the subjects will be asked to bring his/her own mCC and provide his/her anticipated amount of mCC , plus 2 extra packs.

6.1.3 Packaging and Labeling

At Admission (all study subjects), subjects will provide the anticipated amount of mCC in sealed packs to the study site collaborator. The mCC packs provided by the subjects should not be opened and the cellophane wrapper should be intact.

Each pack of mCC provided by the subject will be labeled to identify which subject the cigarettes belong to (labels should be affixed by the study site collaborator to the cellophane wrapper of the lower part of the pack). Each pack of mCCs will be labeled to identify necessary information to match the subject with its suppliers.

For the Menthol Tobacco Sticks, the packs and cartons will be pre-labeled with the necessary information including, but not limited toproduct code. The labels will be translated into Japanese. See Appendix 4.

6.2 Use of Investigational Product(s)

Subjects will never be requested or forced to smoke and will be free to stop smoking at any time during the study. The study is designed as an *ad libitum* use study. During the screening period, subjects will be allowed to smoke according to their smoking habits except during the procedures of the screening Visit at the discretion of the site.

During the confinement period product (mCC or THS 2.2 Menthol) use will generally be allowed between 06:30 AM to 11:00 PM.

During the ambulatory period, there will be no smoking/product restriction except on Day 30 Visit, Day 60 Visit, and Day 90 Visit: on Day 30, Day 60, and Day 90: product use will be allowed from 08:00 AM to 23:00 PM and during the Visit. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted. On Day 31, Day 61, product use will be allowed from 06:30 AM. In the morning of Day 91 after the end of exposure ambulatory period (11:00 PM on Day 90), subjects will not be allowed to smoke CC until CYP2A6, cough and MNWS questionnaires and spirometry have been done on site. The use of THS 2.2 Menthol will be strictly forbidden for subjects in the mCC or SA arms.

6.2.1 Run-in Period

Smoking ad libitum will be allowed prior to admission and throughout the day except during the procedures. All subject s will be allowed to continue smoking *ad libitum* their single preferred brand of usual mCC. All subjects (except women with a positive pregnancy test at Screening or at Admission) will undergo a THS 2.2 Menthol product test prior to enrolment.

Following the confirmation that the subject is able and willing to use the THS 2.2 product, subjects will be enrolled.

6.2.2 Baseline Period

During the baseline period, all subjects will be allowed to continue smoking *ad libitum* their single preferred usual brand of mCC.

6.2.3 Exposure Period

During the exposure confinement period until the time of Discharge on Day 6, subjects will not be allowed to use any nicotine/tobacco-containing products other than their assigned product/regimen. On Day 6, when the safety procedures of discharge will be conducted, the use of product (THS 2.2 Menthol or mCC) will be allowed but after CYP2A6, cough and MNWS questionnaires and spirometry have been done. Smoking will not be allowed in the SA arm.

During the exposure ambulatory period, subjects will be instructed to continue using exclusively their assigned product/regimen. The use of any CCs (menthol or non-menthol) or nicotine/tobacco-containing products other than the product/regimen the subject is assigned to must be documented in the daily product use electronic diary. Subjects in the SA arm will be instructed to abstain from smoking.

In the morning of the Day 91, smoking will not be allowed to smoke until CYP2A6, cough and MNWS questionnaires and spirometry have been conducted at the clinic. After, subjects will be allowed to smoke. On Day 91, safety procedures of Discharge will be conducted prior the time of Discharge of the subject from the site (completion of the study).

During the study, any subjects who is willing to stop smoking will be referred for further treatment as per the standard of care in the country in which the study is conducted.

6.2.3.1 THS 2.2 Menthol Arm

During the exposure period in confinement, subjects randomized to the THS 2.2 Menthol arm will use exclusively THS 2.2 Menthol from Day 1, 06:30 AM onwards until time of Discharge on Day 6.

On the time of Discharge on Day 6 and on each ambulatory visit, subjects will be instructed to continue using exclusively THS 2.2 Menthol ad libitum until Day 90 11:00 PM.

6.2.3.2 Menthol Conventional Cigarettes Arm

During the exposure period in confinement, subjects randomized to the mCC arm will continue smoking their mCC from Day 1, 06:30 AM onwards until time of Discharge on Day 6.

On the time of discharge on Day 6, subjects will be informed that they can continue to smoke their mCC ad libitum if they wish until the time of Discharge on Day 90 11: 00 PM.

6.2.3.3 Smoking Abstinence Arm

During the exposure period in confinement, subjects randomized to the SA arm will be instructed to abstain from smoking from Day 1, 06:30 AM until the time of Discharge on Day 6. They will not be provided with medication supportive for smoking abstinence.

On Day 6 and on each ambulatory visit and at any appropriate occasion, subjects in the SA arm will be instructed to remain abstinent with or without NRT until time of discharge of Day 91.

6.2.4 Stopping Rules for Investigational Product

For safety purposes, smoking 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.

6.2.5 Safety Follow-up Period

During the safety follow-up period (after the Time of Discharge at Day 91 until Day 119), subjects in the THS 2.2 Menthol and mCC arms are free to smoke their own mCC *ad libitum*. Subjects in the SA arm who wish to continue their SA, will be referred for further treatment as per the standard of care in the country in which the study is conducted, if requested by the subject. If subjects in the SA arm cannot refrain from smoking, they may start smoking their own brand of mCC after the time of Discharge at Day 91.

6.3 Method for Assigning Subjects to Study Arms

When all the eligibility criteria have been met, randomization will be done through the Interactive Web and Voice Response System (IWRS) on Day 0 at any time during the day. Subjects will be informed of their randomized study arm in the morning of Day 1, prior to 06:30 AM.

Subjects will be randomized to one of the three study arms THS 2.2 Menthol:mCC:SA in a 2:1:1 ratio. Stratified randomization will be conducted by sex and by daily average cigarette consumption in the 4 weeks prior to the Screening Visit (those smoking 10 to 19 CC and those smoking >19 CC per day) reported by the subject. In each arm, each sex and each of

the smoking strata should have a quota applied to ensure they represent at least 40% of the population.

6.4 Blinding

This is an open-label study; therefore, the subjects and Investigator will be unblinded to the subject's arm. 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 arm as summarized in the following table:

Blinded Study Personnel	End of Blinding Period
PMI and CRO study statisticians	After the statistical analysis plan (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 scientists	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 (QC) activity, data listings will be reviewed by PMI before database lock, with no access to the randomization arm information.

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

6.5 Investigational Product Accountability and Compliance

6.5.1 Dispensing Investigational Product

From Day-2 onwards during the confinement period, each mCC will be dispensed to the subjects one by one. Subjects in the THS 2.2 Menthol arm will be provided by the site study collaborators with Menthol Tobacco Sticks from Day 1 to Day 5 stick by stick. One mCC/Menthol Tobacco Stick will be allowed at a time, as per the study design, and documented in an appropriate Log.

On each day of the confinement period, the time of dispense and return for each product has to be documented from Day-1 for CC and from Day 1 for Menthol Tobacco Sticks onwards. The start of product use will correspond to the time of dispense of the first mCC/Menthol Tobacco Stick. The subject must not take a puff of the Menthol Tobacco Stick during the

pre-heating time. The product will not be promoted for commercial distribution or test market.

During the ambulatory period, subjects in the THS 2.2 Menthol arm will be provided with an anticipated amount of Menthol Tobacco Sticks to cover the period until the next study visit. An additional number of Menthol Tobacco sticks will be dispensed to the subjects at these visits to cover for any unexpected delay to the visit schedule made by the subject. Extra delivery of THS Menthol Tobacco Sticks in between two visits may be envisaged. Subjects in the mCC arm and will buy their mCCs directly from shops.

6.5.2 Storage and Accountability

The study collaborator (the IP product storage manager) designated by the head of the investigational site will be responsible for the storage and accountability of the IPs in accordance to sponsor's requirements.

The THS 2.2 Menthol and mCC will be stored in a secured storage site with access limited to authorized personnel only. Full accountability of the distributed products will be ensured by designated IP storage manager.

6.5.2.1 Confinement Period

On each day of the confinement period, study collaborators will record on the Accountability Log every occasion from Day -1 to time of Discharge on Day 6 that mCCs are dispensed to a subject by the study collaborator and every occasion from Day 1 to time of Discharge on Day 6 that the THS 2.2 Menthol product components (i.e. THS Tobacco Stick holder, THS charging unit, THS accessories) and Menthol Tobacco Sticks are dispensed to a subject.

Subjects will return each butt of mCC immediately after use from Day -1 to Day 6 for accountability. This will be documented in appropriate log.

Immediately after use, all tobacco plugs of all used Menthol Tobacco Sticks will be separated from the filters and the tobacco plugs and the filters will be collected from Day 1 to Day 5, using dedicated vials for accountability and subsequent analysis of potential combustion occurrences and nicotine retained in the filters (see also Section 7.8.2). This will be documented in an appropriate log.

6.5.2.2 Ambulatory Period

THS 2.2 Arm:

Subjects must return any empty packs and partially used packs of Menthol Tobacco Sticks they have used during the preceding weeks to the site for accountability. After accountability they will be destroyed at study completion in accordance with sponsor's requirements.

All tobacco plugs from Menthol Tobacco Sticks used after check-in to the investigational site until 11:00 PM on Day 30, Day 60, and Day 90 will be collected in dedicated vials for subsequent analysis of potential combustion occurrences. No filter analysis of the Menthol Tobacco Sticks will be conducted during the visits of the ambulatory period.

mConventional Cigarettes Arm:

No IP accountability will be done for mCC.

Smoking Abstinence Arm:

No IP accountability will be done for SA arm.

6.5.3 Investigational Product Retention

The study site will destroy or return to the Sponsor any unused Menthol Tobacco Sticks and will return to the Sponsor the THS 2.2 Menthol product components upon study completion. Retention of THS 2.2 Menthol products will be documented.

Irrespective of the study arm on the time of Discharge from the clinic, the study collaborators will return to the subjects any remaining mCCs given to them on the day of Admission.

6.5.4 Compliance to Investigational Product

During the confinement period, compliance for all study arms will be ensured by strict dispensation of the products (product by product) and collection of used Menthol Tobacco Sticks/CC butts will be documented in appropriate log..

During the ambulatory period, subjects in the 3 study arms will capture, from the time of Discharge on Day 6 to Day 90 11:00 PM the number of product used (e.g., menthol and non-menthol CC, Menthol Tobacco Sticks, or any other tobacco /nicotine-containing products including NRT) on a daily basis in the product use electronic diary. The product use electronic diary will be supplied by Sponsor and distributed to the subjects by the study site collaborator. The product use electronic diary will serve as a compliance tool in the three arms. On Day 6, the compliance to the product will be ensured by the merge of the

accountability log (from 06:30 AM to time of discharge) and the product use electronic diary. In case of discrepancy between the log and the electronic diary entries, the electronic diary entries will be considered as source of data.

In addition, in the SA arm, compliance will be chemically verified using an exhaled CO breath test during both the confinement and ambulatory periods. The cut-off point for the CO breath test value to distinguish mCC use versus no mCC use will be 10 ppm (Benowitz et al., 2002).

6.6 Restrictions

6.6.1 Smoking Restrictions and Restrictions to the Smoking Abstinence Arm

6.6.1.1 Confinement Period

To avoid smoke cross contamination between the three study arms, subjects in the THS 2.2 Menthol and the mCC arm must smoke in separate rooms and subjects allocated to the SA arm should not have access to the smoking rooms. All precautions should be taken to remove any temptation to smoke for subjects who are randomized to the SA arm.

In the THS 2.2 Menthol and SA arms, subjects will not be allowed to smoke any mCC or use any nicotine/tobacco-containing products (including NRT) from Day 1 (06:30 AM) until the time of Discharge on Day 6. In the mCC arm, subjects will not be allowed to use the THS 2.2 Menthol, any nicotine/tobacco containing products other than mCC brought to the site by the subject to the site. In the SA arm, intensive support including psychological support will be provided upon the request of the subject or of the Investigator or study site collaborator.

Smoking will generally only be allowed during the designated smoking times, from 06:30 AM to 11:00 PM. Smokers will not have free access to their mCC or THS 2.2 Menthol; these will be dispensed by the study collaborator individually as described in Section 6.5.1.

From admission on site, smoking will not be allowed during assessments on the Admission Day at the discretion of the site. Smoking will be allowed on Day 6 after CYP2A6 activity measurements, assessment of cough and MNWS questionnaire completion and spirometry,have been conducted.

In general, the performance of scheduled procedures has priority over the wish of a subject to use the product. However, this is different at Day 5 due to the assessment of the nicotine profile. If the subject wants to use the product at Day 5 around the time of the blood draw, he/she should use the product first and the blood will be drawn after product use.

6.6.1.2 Ambulatory Period

Subjects in the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects in the SA arm will be instructed to remain abstinent from smoking with or without NRT. Subjects in the SA arm may use NRT if considered necessary by the Investigator or if requested by the subject. NRT products will be used as per the product label, and may be purchased by subjects at a pharmacy. Subjects will be reimbursed. Intensive support including psychological support will be provided upon the request of the subject or of the Investigator or study collaborator.

Product use will be allowed during the ambulatory visits from 08:00 AM to 11:00 PM on Day 30 and Day 60, and on Day 90. On Day 31, and Day 61, product use will be allowed from 06:30 AM. However, in the morning of Day 91, smoking will not be allowed until assessment of cough and MNWS questionnaires completion and CYP2A6 and spirometry, have been performed on site.

6.6.2 Dietary Restrictions

6.6.2.1 Confinement Period

A standard diet will be designed by a dietician. For each meal, the caloric and fat content should be controlled in order to avoid “high-fat” diet. The FDA guidance on food-effect studies for bioequivalency testing identifies a “ high-fat” diet as a diet which maintains approximatively 50 percent of total caloric content of the meal and is high in calories (approximately 800 to 1000 calories) (FDA, 2002).

In order to avoid any effect on assessment of BoExp, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage will not be permitted (Tiffany et al., 1991). In addition, to avoid any effect on the measurement of CYP1A2 activity, alcohol, broccoli, brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) will be forbidden (Faber et al., 2004) (except for the intake of the caffeine tablet for CYP1A2 measurement). Consumption of quinine-containing drinks (e.g., tonic water) is not allowed.

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 snack, fruits, and raw vegetables can be distributed to the subjects without restrictions at any time during confinement as long as they fulfill the above requirements described in this section. Consumption of water is allowed as desired. The same menu and meal schedule will be administered uniformly for all subjects in all study arms. In addition for the purpose of the Ames test planned on Day 0 and Day 5, the menus served on Day-1 and Day 4 will be identical.

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

1. safety laboratory on screening, Day 0, Day 6
2. risk marker in serum/plasma/blood on Day 0 and Day 6.
3. serum/plasma bio-banking samples for further analysis of BoExp and risk markers at the Screening Visit, on Day 0, Day 6.
4. blood bio-banking for transcriptomics on Day 0, Day 6.

6.6.2.2 Ambulatory Period

The above dietary restrictions are not applicable for the ambulatory period. However, 3 days prior to the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, and during visits on site, subjects will be asked by the study collaborators to refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the ambulatory visits.

A fasting state has to be observed for at least 10 hours prior to blood draws for:

1. safety laboratory on Day 31, Day 61, and Day 91
2. risk factor assessments in serum/plasma/blood on Day 31, Day 61 and Day 91.
3. serum/plasma bio-banking samples for further analysis of BoExp and risk markers on Day 91.
4. blood bio-banking for transcriptomics on Day 91.

6.7 Concomitant Medication

No medication should be taken during the study from the screening to the time of discharge on Day 91 without prior informing the Investigator. However, the Principal Investigator is responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescribing of medication will be made in the best interests of the subject.

During the ambulatory period, subjects in the SA arm may use NRT on the judgment of the Investigator or on request of the subject. No medication supportive for smoking cessation other than NRT will be allowed in the study.

Concomitant use of NSAIDs and acetylsalicylic acid (including over-the counter products) is not allowed, as all of them could interfere with risk markers such as 11-DTX-B2. Paracetamol will be allowed at a daily total dose of up to 1500 mg. Any medication with an

impact on the CYP1A2 and CYP2A6 metabolism (as prescription and over-the-counter products) as shown in Table 3 must be avoided.

If the use of a concomitant medication cannot be avoided for the subject's safety, it must be fully documented in the Source Document and transcribed into the eCRF (for details, see Section 7.4.5)..

The drugs and substances shown in Table 3 are a selection of drugs considered to have an impact on CYP1A2 and/or CYP2A6 activity (Chang et al., 1999, Ingelman-Sundberg et al., 1999, Lacy et al., 2007). Prior to database close, concomitant medication will be assessed according to their potential impact on CYP1A2 and CYP2A6 activity and potential impact on the study results.

Concomitant medication will first be assessed at Screening Visit. To be eligible for the study, any medication with impact on CYP1A2 and CYP2A6 metabolism must be discontinued at least 2 weeks prior to Admission to the clinic or for at least 5 half-lives (whichever is longer). They must not be used during the entire study until the time of discharge on Day 91 (completion of the study).

Medication containing estrogens (e.g. for contraception and for hormone replacement therapy), even though known to be CYP1A2 inhibitors, will be allowed in this study but must be documented on the eCRF.

Table 3. Examples of Medications with effects on CYP1A2 and CYP2A6 activity

Drug name	Substance Class
Fluoroquinolones, including ciprofloxacin and ofloxacin, nafcillin, rifampicin	Antibiotics
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	H_2-receptor antagonist
Amiodarone, verapamil, mibefradil, mexiletin, propafenone, propanolol, lidocaine	Antiarrhythmic
Losartan, amlodipine, nifedipine,	Antihypertensive
Drospirenone, estrogens	Hormonal contraception, 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
Modafinil, diclofenac, rofecoxib	Analgesic
Insulin	Anti-diabetic
Sildenafil	Erectile dysfunction
Quinine	Leg cramps
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 source: Chang et al., 1999, Ingelman-Sundberg et al., 1999, Lacy et al., 2007. The list is not exhaustive.

7 STUDY PROCEDURES

Personnel performing study measurements or recordings must have the appropriate training fully documented. Quality and control measures have to be in place. An overview of all study procedures is shown in the Schedule of Events (Appendix 1). In this Section, only the expected/planned time points for the various measurements are described. As not all subjects can undergo a procedure at the same time, adequate time windows are given for each study procedure and each time point (see Section 9). Study collaborators will adhere to the site's Standard Operating Procedures (SOPs) for all activities. Appropriate medical advice will be provided to the subject in case of any medial findings requiring health care.

7.1 Informed Consent/Subject Information Sheet

Prior any study assessments is performed, the subject will be asked to provide his consent to participate to the study (ICF for study participation) (Section 1.3).

In addition to the ICF for study participation, the subject will be asked to provide his separate consent for two kinds of biobanking (Sections 1.3.2).

- ICF to the additional bio-banking of serum/plasma/urine samples for further measurements of BoExp and risk markers.
- ICF to the additional bio-banking of blood sample for further transcriptomics (pharmacogenomics) analysis.

The subject's participation in the study does not depend on their consent for both bio-banking for BoExp of exposure/risk markers and for pharmacogenomics analysis) will be separate to that for study participation. The three consents will be captured in the eCRF.

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

Each subject will be given advice on the risks of smoking six times during the study: at the Screening Visit, at Admission (Day -2), at Day 6, and at Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91). This will take the form of a brief interview according to WHO recommendations (Raw et al., 2002). 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 dedignee 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.

7.3 Support for the Smoking Abstinence Arm

All subjects in the SA arm will be closely monitored from Day 1 onwards until Day 91 by the study collaborators for possible signs and symptoms of nicotine withdrawal. This includes clinical monitoring e.g. vital signs, physical examination, and body weight. It also involves close monitoring of the subject's behavior, mood, and any AEs. A psychologist may be contacted and will be available upon subject's request, or if considered necessary, upon the request of the Investigator or study site collaborator.

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 e.g. 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 no. 04 is still fulfilled.

7.4.1 Demographic Data

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

7.4.2 Identification of the Current Cigarette Brand

Identification of the current mCC brand(s) smoked by the subject will be done at the Screening Visit and at Day -2. At the Screening Visit, smokers will be asked to bring a pack of their current mCC brand(s) to the site. On Day -2, subjects will hand their mCC supply for the entire confinement period to the study collaborators. The study collaborator will document the brand name and yields. A photograph of the front and the side of the cigarette pack supplied by the subject (bearing the tar, nicotine) will be taken by the study collaborators in addition to recording the brand name and yield. These photographs will be considered as Source Documentation. A copy of the photographs will be provided to the Sponsor electronically (as Digital Video Disk or Compact Disk).

7.4.3 Smoking History and Willingness to Quit Smoking

Subjects will be asked about their smoking history. At Screening and on the Day of Admission (Day -2), this will include questions to evaluate whether the subject has smoked for at least the last three consecutive years, to determine the number of mCC smoked during the previous 4 weeks, and to check if the CCs smoked during the previous 4 weeks were mCCs. At the Screening Visit only, the subject will also be asked if he/she plans to quit smoking within 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.

At Screening and on the day of Admission (Day -2), subjects will also be asked if they are ready to abstain from smoking for up to 90 days (as required in the study protocol inclusion criteria number 7). Only subjects who are prepared and able to comply with this requirement will be considered for participation in the study.

7.4.4 Demonstration and Trial of the THS 2.2 Menthol

All subjects will be shown a demonstration of the THS 2.2 Menthol product at the Screening Visit. On Day -2, as the last procedure of the eligibility assessments on that day, subjects will be offered a product test of the THS 2.2 Menthol (using of up to 3 Menthol Tobacco sticks). In female subjects, the THS 2.2 Menthol test must only be done after pregnancy is excluded by a negative urine pregnancy test. Enrolment takes place after all requested inclusion and exclusion criteria have been satisfactorily met at Day-2. Only subjects who are willing and able to use the product can participate in the study. The product test will be the last assessement prior to enrolment.

7.4.5 Product Preference

In order to perform a complementary analysis on subjects' preference, the following question will be asked on Day -2 after enrolment to all subjects.

Which product would you prefer to be randomized to:

- THS 2.2 menthol.
- mCC.
- SA.
- no preference.

7.4.6 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical history will be documented at the Screening Visit. 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.

Prior medication taken 4 weeks prior to Screening Visit 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 of any medication taken must include the drug name (preferably both generic and trade name), route of administration (e.g. oral, intravenous), total daily dose/unit (e.g. expressed in mg, ml, or IU), indication, the start and (if applicable), the stop date (day, month and year). Any therapy changes (including changes of regimen) during the study are to be documented. Any concomitant medication that is still being taken by the subject at the end of the study will be recorded on the eCRF.

7.4.7 Physical Examination

A physical examination will be conducted at the Screening Visit, at Admission (Day -2), at Discharge from the clinic on Day 6, on Day 30 Visit (Day 30), Day 60 Visit (Day 60), and on Day 90 Visit (Day 91).

7.4.8 Body Height Weight and Waist Circumference

Body weight will be recorded on the Screening Visit, on Admission (Day -2), on Discharge on Day 6, on Day 30 Visit (Day 30), Day 60 Visit (Day 60), and on Day 90 Visit (Day 91). Body height will be measured only at the Screening Visit. Waist circumference will be measured on Admission (Day -2) and on Day 90 Visit (Day 91). Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

Body mass index (BMI) will be calculated from the body weight and height using the following formula:

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

height in meters^2

Weight and waist circumference will also be analyzed as risk markers (Section 7.5.2.1).

7.4.9 Vital signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate will be measured at the Screening Visit, at Admission (Day -2), in the morning of every day of the confinement period (i.e., Days -1 to 6), and at each ambulatory visit (Day 30 Visit on Day 30, Day 60 Visit on Day 60 and Day 90 Visit on Day 91). All measurements will be made after the subject has rested for at least 5 minutes in a supine position. For every measurement, it will be documented if the subject has smoked within 15 minutes prior to the measurement.

Systolic and diastolic blood pressure will also be analyzed as risk markers (Section 7.5.2.1).

7.4.10 Other Clinical Assessments

7.4.10.1 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. At screening, spirometry has to be conducted at least 1 hour after smoking. Furthermore, spirometry without bronchodilator will be performed prior to product use at Day 0 (baseline values), on Day 6, and Day 90 Visit (Day 91) (for comparison with the baseline values).

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. Spirometry predicted values will be standardized to the NHANES III predicted set.

All personnel performing lung function testing should have the appropriate training and quality control (QC) measures should be put into place and be properly documented and filed at the pulmonary function laboratory (including the records of the calibration, if applicable). The FEV_1 and FVC will be recorded.

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

For spirometry, assessed parameters will include:

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

7.4.10.2 Electrocardiogram

An Electrocardiogram (ECG) will be recorded at Screening, on Day 6, at Day 30 Visit (Day 30), Day 60 Visit (Day 60), and at Day 90 Visit (Day 91). ECG testing will be performed as per the site's local practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval and QTc interval corrected by the ECG machine 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 on the eCRF for all ECGs assessed as abnormal – clinically relevant. All ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the Source Documents.

7.4.10.3 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 will be carried out using validated methods (see Sections 7.6 and 7.7). The bioanalytical methods used will be documented in the Bioanalytical Plans/Reports. A list of laboratories is provided in Appendix 2.

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

7.5.1 Biomarker of Exposure

7.5.1.1 Exhaled CO and Carboxyhemoglobin

Carboxyhemoglobin measured in blood and exhaled CO will be investigated as a measure of exposure to CO in all three study arms. A CO breath test should be conducted in timely conjunction with the blood sampling for COHb, where applicable. In the SA arm, the CO breath test will serve as a verification of compliance. (Section 6.5.4).

CO Breath Test

Carbon monoxide in exhaled breath will be measured using the Smokerlyzer® device such as Micro 4 Smokerlyzer® device or similar in all 3 study arms.

During the confinement period on Days -1 to Day 5, the CO breath test will be conducted four times per day. The first assessment should be conducted within 15 minutes prior to the first product use. The other 3 assessments should be conducted as described in Section 9.

For subjects in the SA arm from Day 1 onwards, the first CO breath test will be done at between 08:00 AM-09:30 AM. The other 3 assessments should be conducted as described in Section 9.

On Day -2 and Day 6, and during the ambulatory period on Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90), the CO breath tests will be conducted once, irrespective of time of product use.

Carboxyhemoglobin

COHb measurement will be performed in all 3 study arms at a local laboratory. Carboxyhemoglobin will be assessed on a daily basis from Day-1 until Day 5.

On Day -1 to Day 4: one blood sample will be collected in the evening between 8:00 PM-09:30 PM.

On Day 5: one blood sample will be collected within 15 minutes prior first product use. The three other blood samples will be collected as described in Section 9.

For subjects in the SA arm from Day 1 onwards, the first COHb will be done between 08:00AM-09:30 AM. The three other blood samples will be collected as described in Section 9.

On Day 30 Visit (Day 30), Day 60 Visit (Day 60)and Day 90 Visit (Day 90): for all study arms, one blood sample will be collected during the visit, irrespective of the time of product use.

7.5.1.2 Plasma Nicotine and Cotinine

Nicotine and cotinine concentrations will be measured in plasma to evaluate the exposure to nicotine in all three study arms. No sampling for PK profile will be done for subjects in the SA arm (Day 5 to Day 6) and only one blood sampling will be done both on Day 5 and Day 6.

- On Day 0 to Day 4 (all study arms):

  One blood sample per day will be taken in the evening between 08:00 PM-09:30 PM.

- Nicotine/cotinine Pharmacokinetic (PK) Profile on Day 5 and Day 6 (THS 2.2 Menthol and mCC arms only):

  In total, nine blood samples will be drawn on Day 5. The first blood sample on Day 5 will be drawn within 15 minutes prior the first product use. On Day 5, the start time of the first product use (T0) will serve as reference for the time to peak concentration. An additional eight blood samples will be drawn in 2 hour intervals after the start of product use. The last blood sample should be drawn no later than 11:00 PM, corresponding to the end of product use. At all time points, if the subject wants to use the product around the time of the blood draw, he/she should use it first and the blood will be drawn after product use. Depending on the time of the first product use, it may be that fewer than eight blood samples will be collected from a subject after T0.

  On Day 6, two blood samples will be drawn. The first one will be 20 hours after T0 and the second blood sample will be 24 hours after T0 (with T_0 being the start time of first product use at Day 5).

- On Day 5 and Day 6 (SA arm only):

  On Day 5, one blood sample will be drawn in will be taken in the evening between 8:00 PM-09:30 PM.

  On Day 6, one blood sample will be drawn between 08:00 AM-09:30 AM.

- On Day 30 Visit (Day 30), Day 60 Visit (Day 60), Day 90 Visit (Day 90) (all study arms):

  One blood sample will be drawn during these visits, irrespective of the time of product use.

7.5.1.3 Other Biomarkers of Exposure

BoExp will be measured as per the Schedule of Events (see Appendix 1):

- in 24-hour urine collection samples during the confinement period from Day -1 onwards to Day 5.
- in 24-hour urine collection during the ambulatory period collected on Day 30 Visit, on Day 60 Visit, and on Day 90 Visit.

The following BoExps will be measured:

- Selected primary BoExp: MHBMA, 3-HPMA, S-PMA, and total NNAL
- Selected secondary BoExp: Total 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, NEQ, CEMA, 3-hydroxybenzo(a)pyrene, HEMA, S-BMA and HMPMA.

For normalization of BoExp, creatinine will also be measured in the 24 hour urine samples.

7.5.2 Other Assessments

7.5.2.1 Risk Markers

The following risk markers will be assessed in this study:

- Systolic and diastolic blood pressure, hs-CRP, fibrinogen, homocysteine, blood glucose, LDL, HDL, TG, TC, HbA1c, sICAM-1, WBC, 8-epi-PGF2α, 11-DTX-B2, platelet count, weight, and waist circumference.

The assessment of systolic and diastolic blood pressure, blood glucose, TG, TC, platelet count, weight, and waist circumference will not be repeated because there are part of the safety parameters or clinical evaluation.

Selected risk markers will be evaluated at the following time points in at least 10-hour of fasting state conditions for the assessments which require blood, serum, or plasma:

- Systolic and diastolic blood pressure: to be evaluated as risk markers on Day 0, Day 6, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 91)..The results from vitals signs will be used.
- hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC in serum: to be evaluated as risk markers on Day 0, at Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91). Samplings will be planned to measure hs-CRP, homocystein, LDL, HDL

at the mentioned timepoints. The results on blood glucose, TG, and TC from the safety laboratory panel on Day 0, Day 31, Day 61, and Day 91 will be used.

- Fibrinogen in plasma: to be evaluated as risk markers on Day 0, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91). Samplings will be planned to measure fibrinogen at the mentioned timepoints.
- HbA1c in serum: to be evaluated as risk markers on Day 0, and Day 90 Visit (Day 91). Samplings will be planned to measure HbA1c at the mentioned timepoints.
- sICAM-1 measured in serum: to be evaluated as risk markers on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91). Samplings will be planned to measure sICAM-1 at the mentioned timepoints.
- 8-epi-PGF2α and 11-DTX-B2 in urine: to be evaluated as risk markers in 24-hour urine on Day 0 and Day 5 and in 24-hour urine collection on Day 30 Visit, Day 60 Visit , and Day 90 Visit. Samplings will be planned to measure 8-epi-PGF2α and 11-DTX-B2 at the mentioned timepoints. The results will be normalized to creatinine and express as concentration adjusted to creatinine.
- WBC and platelet count in whole blood: to be assessed as risk markers on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91). The results from the safety laboratory panel will be used.
- Waist circumference and weight: to be assessed as risk markers on Day-2 on Day 90 Visit (Day 91)as evaluated as part of the clinical examination (see Section 7.4.8).

7.5.2.2 CYP1A2 activity test

CYP1A2 activity will be measured on Day 0, Day 5, and Day 90 Visit (Day 90). Measurement of enzyme activity will be based on the post-dose PX and CAF plasma molar concentrations approximately 6 hours (±15 minutes) after the intake of one Tomerumin® (LionCorp.) caffeine tablet (around 170mg caffeine) with 150 ml ±10 ml water (Faber et al., 2004).

The exact time of intake of the caffeine tablet in the morning and of the time of blood sampling (the blood sample will be taken 6 hours [±15 minutes] after the intake of the tablet) must be recorded. CYP1A2 activity will be assessed by measuring PX and CAF and calculating the PX/CAF molar metabolic ratio (Faber et al., 2004).

7.5.2.3 CYP2A6 activity

CYP2A6 activity will be measured in plasma on Day 0, Day 6, and Day 90 Visit (Day 91), using the molar metabolic ratio of *trans*-3'-hydroxycotinine and cotinine (Jacob et al., 2011).

Blood sampling for CYP2A6 has to be done prior to product use. CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites.

7.5.2.4 Ames Mutagenicity Test

Urine mutagenicity, a biomarker for measuring mutagen load, will be measured on Day 0, Day 5 and on Day 90 Visit in 24-hour urine. The urinary determination of each sample will be done in one bacterial strain (*S. typhimurium* strain YG1024), using S9 metabolic activation and 4 doses for each of the urine extracts.

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, Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and at Day 90 Visit (Day 91). Blood samples will be taken after at least 10 hours of fasting (see Section 6.6.2). The urine test will be performed semi-quantitatively as a urine test. Parameters to be measured are listed in Table 4.

Table 4. Clinical Laboratory Parameters for Safety Panel

Hematology	Clinical Chemistry	Urine analysis

- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count
- Differential WBC count:
  • Neutrophils
  • Basophils
  • Eosinophils
  • Lymphocytes
  • Monocytes
	- Albumin
	- Total protein
	- Alkaline phosphatase (AP)
	- Alanine aminotransferase (ALT)
	- Aspartate aminotransferase (AST)
	- Blood urea nitrogen (BUN)
	- Creatinine
	- Gamma-glutamyl transferase (GGT)
	- Fasting Glucose
	- Lactate dehydrogenase (LDH)
	- 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 human immunodeficiency virus (anti-HIV1/2 and p24 antigen) will be done at Screening.

7.6.3 Urine Drug Screen

A urine drug screen will be performed at the study site at the Screening Visit and on the day of Admission (Day -2). The urine will be screened for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

7.6.4 Urine Cotinine Screening

A urine cotinine test will be performed at Screening and at Admission to the clinic (Day -2) in order to confirm the subject's smoking status. The test must detect cotinine with a cotinine threshold of ≥200 ng/mL.

7.6.5 Alcohol Breath Test

Subjects will have a breath alcohol test at the Screening Visit and at Admission to the clinic (Day -2) using an alcometer device.

7.6.6 Urine Pregnancy Testing

All female subjects will undergo pregnancy testing at the Screening Visit, at Admission (Day -2), at Day 6, at Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91). Female subjects with a positive pregnancy test at the Screening Visit or at Day -2 cannot be enrolled and will be considered a screening failure. The product test at Admission must be done only in female subjects with a negative urine pregnancy test. In any case of a positive urine pregnancy test, the Investigator will inform the subject about the risks associated with smoking during pregnancy. In the event of an unclear urine pregnancy test, 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 Sampling Handling and Storage

All blood samples are to be tested at a central laboratory with the exception of COHb blood sample and the safety laboratory panel which will be tested at a local laboratory (see Appendix 2). The urine test for urine pregnancy tests, urine drug screen, and urine cotinine tests will be done by personnel at the study sites.

Detailed procedures for sample collection and handling of samples are described in a separate Sample Handling Manual (SHM). Safety laboratory samples will be destroyed as per the laboratory's standard procedures. All other samples (except bio-banking samples) will be destroyed after 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 will be allowed.

The bioanalytical lab(s) are listed in Appendix 2.

7.7.1 Blood samples

Blood samples will be collected by qualified and trained site personnel. Subjects should be in a seated position during blood collection. The maximal total volume of blood drawn for each subject will around 290 ml, which includes 50 ml for safety and repeated analysis, 30 ml of blood for long term storage of the bio-banking samples for further anaylsis of BoExp and risk markers (only if additional consents are given) and 15 ml for long-term storage bio-banking

samples for further analysis of transcriptomics (only if additional consents are given) (see Section 7.7.3).

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

7.7.2 Urine samples

Spot urine samples will be used for the urine drug screen, urine cotinine screen, urine pregnancy test, and safety urinalysis.

24-hour urine collection during the confinement period:

For the 24-hour urine collection, subjects will empty their bladders shortly before 06:30 AM on the study day indicated in the Schedule of Events (Appendix 1). The collection period starts at 06:30 AM and ends on the following day at 06:29 AM. Shortly before 06:29 AM, after nearly 24-hours of urine collection, subjects will empty their bladder again and this urine will be used as the final portion of the 24-hour urine sample.

At time of Discharge on Day 6, subjects will empty their bladder shortly before 06:29. This will be the last urine portion for the 24-hour urine for the Day 5 dot mark in the Schedule of Events.

24-hour urine collection during the ambulatory period:

Twenty four-hour urine fraction will be collected on Day 30 Visit, Day 60 Visit, and Day 90 Visit) at site.
Subject will be asked to come at site at around 08:00 AM on Day 30, Day 60 and Day 90 and will remain overnight on site until respectively Day 31, Day 61, and Day 91. Subject will be asked to empty his bladder on Day 30, Day 60, and Day 90 shortly before 09:00 AM minutes (this urine will be discarded). Then collection period will start at 09:00 AM ± 20 minutes. After nearly 24-hours of urine collection the day later at 08:59 AM ± 20 minutes, subjects will empty their bladder again and this urine will be used as the final portion of the 24-hour urine sample.

For both confinement and ambulatory periods;

All urine passed during the sampling period must be collected and put into the sampling bottle, with the exception of about 10 mL for the spot urine tests (described above). No urine

must be passed into the toilet. The volume of 24-hour urine, the start and the end time of urine collection will be recorded by the study collaborators.

For assessment of urine BoExp, creatinine for normalization of urine BoExp, 8-epi-PGF2α and 11-TBX-B2, sample bio-banking and urine mutagenicity, aliquots from the 24-hour urine collection will be taken. In the Schedule of Events for the 24-hour urine collection (see Appendix 1), the dot corresponds to the day on which the 24-hour urine collection period starts. For example, for NEQ measured at Day 30 Visit in the 24-hour urine collection that starts on Day 30 and ends later on Day 31.

7.7.3 Bio-banking Long Term Storage of Blood or Urine

If a subject gives consent for sample bio-banking for further analysis of BoExp/risk markers, additionnal samples of urine (from the 24-hour urine collection) and serum/plasma (30 ml of blood in total) will be collected as follows:

- Samples from the 24 hour urine will be collected from the urine collections that started on Day 0, Day 5, and Day 90 Visit (10 tubes of 10 ml each per time points).
- Serum/plasma will be collected on Day 0, Day 6, and Day 90 Visit (30 ml of blood in total with 2 tubes of 5 ml of blood drawn per timepoint: from one tube two x 1 ml plasma and from the second tube 2 x 1 ml of serum will be collected and stored).

If a subject gives consent for sample biobanking of whole blood for further transcriptomics analysis, a total of 15 ml of blood will be collected as follows:

Blood will be collected on Day 0, Day 6, and Day 90 Visit (15 ml in total with 5 ml per timepoint. The 5 ml will be split into two tubes of 2.5 ml each).

The samples intended for sample bio-banking will be kept frozen, separate from the other samples collected, and will be shipped to a central storage facility according to the SHM. After the final CSR is signed, samples of plasma/serum/blood will be stored for a maximum of 5 years and samples of urine will be stored for a maximum of 2 years. The blood bio-banking for transcriptomics will be stored for a maximum of 5 years.

The facility at which the samples are stored will follow their procedures for destruction of banked samples if a subject withdraws their consent for coded sample bio-banking.

7.8 Other Study Procedures

7.8.1 Product Use Diary

A product use electronic diary will be used for the documentation of used Menthol Tobacco Sticks, smoked CCs (menthol and non-menthol), used NRTs product, or the use of other nicotine/tobacco containing products. All subjects (including those subjects randomized to the SA arm) must complete this diary on a daily basis from the time of Discharge on Day 6 until Day 90 11:00 PM Subjects will be trained by the study collaborators in the use of this electronic diary during the confinement period at the time the diary is delivered to the subject by the study collaborator (Day 6).

7.8.2 Human Smoking Topography Assessment

Human smoking topography (HST) involves the measurement of each smoker's unique way of smoking mCCs or using Menthol Tobacco Sticks using the HST SODIM® device. The HST SODIM® device, model SPA/M (SODIM® Instrumentation, Fleury les Aubrais, France) is a device which is used to measure smoking topography (see Appendix 5). It consists of a special sample holder (containing a constriction in the middle) which is placed between the smoker's mouth and the filter of the mCC or menthol THS Tobacco Stick being smoked/used. The holder is connected by two narrow tubes to a portable data logger/recording system (see Appendix 5) for a description of the device.

At Day 0, the HST SODIM® device has to be used for all mCC smoked for all subjects. On Day 1 and Day 4 of the confinement period the HST SODIM® device has to be used for every smoking event for all subjects in the mCC and THS 2.2 Menthol arms. On Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90) of the ambulatory period, HST SODIM® device will start between 08:30 and 09:30 AM with 4 hours recording. Smoking topography with the HST SODIM® device will **not** be done in subjects smoking mCC that are incompatible with the HST SODIM® device (e.g. slim mCC). For subjects in the SA arm, no HST assessments will be performed.

For each subject, one HST SODIM® device will be assigned at Day -1, which will be used by that subject on all HST assessment days (in the case of malfunction, the device will be exchanged). HST SODIM® devices will be assigned to all subjects smoking non-slim mCCs.

The Sponsor will provide training on the use of the HST SODIM® device to the study collaborators. The study collaborators will, in turn, provide training to the subjects. All HST SODIM® devices will be returned to the sponsor after completion of the study.

7.8.2.1 Human Smoking Topography Parameters

The HST SODIM® device measures and records the flow and other per-puff parameters listed in Table 5 below. From the per-puff parameters (Table 5), the per cigarette parameters shown in Table 6 will be derived (representing average values or totals per cigarette).

Prior to calculation of the per-cigarette parameters, the Sponsor HST group will validate the data and discard any invalid data. Only valid data for the per-cigarette parameters will be part of the study database and will be analyzed.

Table 5. Human Smoking Topography – Per-Puff Parameters

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	ml
Puff duration	Di	s
Average flow [Vi/Di]	Qmi	ml/s
Peak flow	Qci	ml/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Work [INT Pmi*FinalFlow*dt]	Wi	mJ
Average pressure drop	Pmi	mmWG
Peak pressure drop	Pci	mmWG
Average resistance [Pmi/Qmi]	Rmi	mmWG/ml/s
Peak resistance [Pci/Qci]	Rci	mmWG/ml/s

Table 6. Human Smoking Topography – Per-Cigarette Parameters

Description	Variable	Formula	Unit
Total number of puffs	NPC	∑ Ni	
Total puff volume	TVOL	∑ Vi	ml
Average puff volume	AvgVi	∑ Vi / NPC, i=1 ... NPC	ml
Average puff duration	AvgDi	∑ Di / NPC, i=1 ... NPC	s
Total puff duration	TDi	∑ Di	s
Average flow	AvgQmi	∑ Qmi / NPC, i=1 … NPC	ml/s
Peak flow	AvgQci	∑ Qci / NPC, i=1 … NPC	ml/s

Description	Variable	Formula	Unit
Total inter puff interval	TIi	∑ Ii	s
Average inter puff interval	AvgIi	∑ Qci / NPC, i=1 … NPC	s
Total smoking duration	TDFi	∑ DFi	s
Total Work	TWi	∑Wi	mJ
Average Work	AvgWi	∑Wi / NPC, i=1 … NPC	mJ
Average pressure drop	AvgPmi	∑Pmi / NPC, i=1 … NPC	mmWg
Average Peak pressure drop	AvgPci	∑Pci / NPC, i=1 … NPC	mmWg
Smoking Intensity	SMINT	TVOL/TDFi	ml/s
Puffing Time Index	PTI	(100*TDi)/TDFi	%
Puff Frequency	PFeq	NPC/(TDFi/60)	Min^{-1}

7.8.2.2 Visual Inspection of The Tobacco Plugs

All tobacco plugs collected during the study will be sent to the Sponsor for subsequent visual inspection to determine whether combustion occurred during product use.

7.8.2.3 THS Filter Analysis

All filters from used Menthol Tobacco Sticks will be sent to an external laboratory for analysis. All filters from used THS Menthol Tobacco sticks will be collected from Day 1 to Day 5. No filter analysis will be done during the ambulatory period.

7.8.3 Questionnaires

The subject questionnaires and the VAS used in this study will be entered by the subject directly in an electronic patient reported outcomes (ePROs) device or on paper copy. All subject reported outcome data will be provided in English and instructions will be provided in the subject's local language. The questionnaires and the VAS will be reviewed for completeness by the study collaborators and subjects will be requested to complete any missing information.

Symptoms or worsening of symptoms documented on any of the questionnaires or the VAS do not need to be documented as additional AEs because the questionnaire and the VAS will be analyzed as part of the final report. However, it is at the discretion of the Investigator to decide whether to document such symptoms as additional AEs. The main source for AE collection will be the face-to-face interview between the subject and study collaborators, using open, non-directive questions (see Section 8.2).

7.8.3.1 Fagerström Test for Nicotine Dependence (revised version)

Potential nicotine dependence will be assessed via a questionnaire at Screening and on Day 90 Visit (Day 90) using the Fagerström Test for Nicotine Dependence (FTND) in its revised version (Fagerström et al., 2012).

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

7.8.3.2 Assessment of Cough

Subjects will be asked to assess the respiratory symptom 'cough' on a VAS, on three Likert scales, and with an open question on a daily basis during the confinement period (from Day 0 to Day 6), and at every visit on Day 30 Visit (Day 31), Day 60 Visit (Day 61) and Day 90 Visit (Day 91). From Day 0 to Day 6 only, assessment of cough must be done prior to start of product use/smoking and no later than 10:00 AM. On Day 30 Visit and Day 60 Visit, assessment of cough will be conducted irrespective of the time of product use but no later than 10:00 AM. On Day 90 Visit (Day 91), assessment of cough will be conducted prior to smoking but no later than 10:00 AM.

Subjects will be asked if they have experienced a regular need to cough, e.g. whether they have coughed several times in the previous 24 hours prior to assessment. If the answer is 'yes', subjects will be asked to complete a VAS, three Likert scales, and to answer the open question.

On the VAS, subjects will assess how bothersome their cough was during the previous 24 hours. The VAS ranges from 'not bothering me at all' to 'extremely bothersome.'

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

The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = very mild – 2 = mild – 3 = moderate – 4 = severe – 5 = very severe.

The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = rarely – 2 = sometimes – 3 = fairly often – 4 = often - 5 = almost always.

The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3, with 0 = no sputum – 1 = a moderate amount of sputum – 2 = a larger amount of sputum – 3 = a very large amount of sputum.

Finally, subjects will be asked with an open question if they want to share any other important observations with the study collaborators about their coughing.

7.8.3.3 Modified Cigarette Evaluation Questionnaire

Product evaluation will be assessed using the Modified Cigarette Evaluation Questionnaire (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, enjoys smoking).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nauseous).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

The MCEQ will be completed by subjects during the confinement period on a daily basis from Day -1 to Day 5 and on every ambulatory visits on Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90). On Day -1 and Day 0, all subjects will complete the questionnaire. From Day 1 onwards, only subjects who are randomized to the THS 2.2 Menthol and mCC arms will complete this questionnaire. The subjects will complete the questionnaire by themselves.

7.8.3.4 Questionnaire of Smoking Urges (QSU-brief)

To assess the urge-to-smoke, all subjects will be asked to fill-in 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 QSU-brief will be completed by the subject himself/herself on a daily basis from Day -1 to Day 5, and on every visit during the ambulatory period, i.e., Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90).

7.8.3.5 Minnesota Nicotine Withdrawal Scale (revised version)

The MNWS revised version is a valid and reliable scale that has been used previously to examine signs and symptoms of withdrawal from cigarette smoking (Hughes et al., 1986, Hughes et al., 2008). It consists of two scales: a ‘self-report scale’ and an ‘observer scale.’

For the purpose of this study, only the self-reporting scale will be used and filled-in by the subject. Furthermore, the subject's weight will not be recorded for the purpose of the MNWS. At the end of the assessment of the questionnaire, the subject's pulse rate will be recorded.

Subjects will be asked to rate the items for the previous 24 hours on a scale ranging from 0 to 4 (where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe).

The MNWS (revised version) will be completed on a daily basis from Day 0 to Day 6, and at every visit during the ambulatory period, i.e., Day 30 Visit, Day 60 Visit and Day 90 Visit. From Day 0 to Day 6 only, MNWS questionnaire must be asked prior to start of product use/smoking and no later than 10:00 AM. On Day 30 Vist (Day 31), and Day 60 Visit (Day 61), assessment of MNWS will be conducted irrespective of the time of product use but no later than 10:00 PM. On Day 91, Assessment of MNWS will be conducted prior to smoking but no later than 10:00 AM

7.8.3.6 HST Questionnaire

A specific questionnaire, used for exploratory purposes has been developed toevaluate the impact of the utilization of the HST SODIM® device on smoker's smoking/inhalation experience in terms of ritual disruption.

This is a questionnaire with five items to be rated on a 5-point scale and open questions. Subjects will be asked by the Investigator to complete the HST questionnaire at:

- On Day 0 for all subjects smoking mCC compatible with the HST device (i.e.,non-slim mCC)
- On Day 4, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90) for all subjects in the THS 2.2 Menthol and mCC arms (except mCC which are not compatible with the HST SODIM® device).

7.8.3.7 Socio-econonomic 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 across 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 4 once they provided informed consent and were enrolled into the study.

On Day 4, subjects will fill a socio-economic status questionnaire. Subjects will be asked a series of questions related to their education, occupation, size and monthly income of their household.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

The FDA MRTP guidelines (FDA, 2011) specify the following definition for adverse events for tobacco products: an AE is any health-related event associated with the use of 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.

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered an IP, which does not necessarily have a causal relationship with the IP. An AE can therefore be any unfavorable and unintended sign (including a clinically relevant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

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 will not be recorded as SAEs (they will be recorded only as AEs). However, 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 End of Study (EOS) either by the Investigator via spontaneous reporting or by the use of consistent, open, non-directive questions from study site collaborator (e.g. "Have you had any health problems since the previous visit/How are you feeling since you were last asked?"). At the discretion of the 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 the face-to-face interview 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 8.2.5.

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' rather than 'fever' and 'hypotension' following blood sample).

Any AE that meets the serious criteria must be recorded both on the AE report form of the case report form (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 Investigators and study site collaborator as described below.

8.2.3 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 collaborators and assessed by the Investigator 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.

8.2.4 Admission Day until the End of Study

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

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 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.

8.2.5 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 activities of daily living (ADL).

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

Severe: The AE is incapacitating and requires medical intervention.

8.2.6 Relationship to Investigational Product and Relationship to Study Procedures

According to the Council for International Organizations of Medical Sciences VI Working Group, there are no definitive methods for distinguishing most adverse drug 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.

In general, all AEs and/or SAEs will be assessed by the Investigator as either 'related' or 'not related' to IP as described below. In addition to the assessment of the relationship of the clinical event to the IP, the 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 administration or a study procedure makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

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

8.2.7 Expectedness

An AE will be regarded as 'unexpected' if its nature or severity is not consistent with information already known about the IP, 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.

8.3 Reporting of Serious Adverse Events

Any 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 28 days after study Discharge), whether or not attributable to the IP, to any other medication or to any study procedures, must be reported by the Principal Investigator **within 24 hours after first awareness by any party** to [redacted] and to the Sponsor, and the head of the Investigational site.

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

[redacted]

Phone number: [redacted]
Toll-free fax: [redacted]
E-mail: [redacted]
Address: [redacted]

Sponsor:
Contact: [redacted]

Phone number: +41 [redacted]
E-mail: [redacted]
Address: Philip Morris Products S.A.
R&D Innovation Cube
5 Quai Jeanrenaud
2000 Neuchâtel
Switzerland

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

Any follow-up information will be detailed in a subsequent SAE Report Form and sent to [redacted] and the Sponsor.

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 is initially reported.

All SAEs will be followed-up by the Investigator until resolution or until the Investigator considers the event to be stabilized (i.e. no worsening of condition), or an acceptable explanation has been found (e.g. 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.

8.4.2 Abnormal Results of Other Tests or Investigations

An ongoing medical condition or clinically relevant finding detected during the Screening Visit (including elevated laboratory parameters), will be considered a concomitant disease and the subject's eligibility for admission to the study will be reviewed.

Any new, clinically relevant, abnormal finding or worsening of a pre-existing condition detected during the study after Screening until the end of the study will be documented as an AE.

Any new onset of symptoms or worsening of pre-existing symptoms identified through the study questionnaires may be documented as AEs at the discretion of the Investigator.

8.5 Reporting and Follow-Up of Pregnancies

For pregnancies detected during the Screening period and prior to first THS 2.2 Menthol use, the subject will be considered as a screening 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 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 EOS must be reported by the Investigator and followed-up. Potential association with exposure to the IP is defined as the conception date being calculated before the 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.

United BioSource Corporation Safety 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 complications, adverse pregnancy outcomes, or maternal complications will be recorded.

The Principal Investigator/head of the investigational site 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 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 THS Charger misuse (use not in accordance with its label and instruction) by a subject, will be documented by the Investigator 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, 2012c):

- 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 unit, etc.) that result in hazards must be documented and reported by the Investigator.

According to FDA medical Device Regulation, data should be collected regarding the use-related hazards that have occurred with 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.

8.8 Investigational Device Malfunction

Any occurrences of malfunction of the Tobacco Stick Holder or Charger will be documented by the Investigator using a Device Issue Log.

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

9 STUDY ACTIVITIES

A detailed schedule of assessment can be found in Appendix 1. 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 procedures 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 -30 to Day -3) prior to admission (Day -2). Subjects will attend the investigational site in at least 10-hour fasting state for clinical laboratory to be assessed. First, the ICF along with study information should be given to the subject. When/if the ICF is signed, the other screening procedures can be performed in the order deemed most practical. While it is recommended to complete as much screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed during screening:

Table 7 shows the assessments that will be performed at the Screening Visit:

Table 7. Time Schedule – Screening Visit

Time	Blood sample	Procedures	Additional information
Start of procedure		**Screening**	
		Informed consent for study participation and two additional consents for bio-bankings	
		Advice on the risk of smoking and debriefing	
		Demographic data collected	
		Identification of current mCC brand	
		Medical history/concomitant disease	
		Prior (within 4 weeks prior to the Screening Visit) and concomitant medication	
		Smoking history	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Screening**	
		Willingness to quit smoking within the next 3 months and to abstain from smoking for up to 90 days	
		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
	√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	To be done after at least 10 hours of fasting
		Urine pregnancy test (all females only)	
	√	HIV, hepatitis B and C	
		Physical examination, and height, weight, calculation of BMI	
		THS 2.2 Menthol product demonstration	
		Chest X-ray (if not performed within 6 months prior to Screening Visit)	
		Urine drug screen	
		Urine cotinine screening test	
		Alcohol breath test screen	
		Fagerström Test for Nicotine Dependence (FTND)	
		Spirometry first without then with short-acting bronchodilator	Has to be done at least 1 hour after smoking
		ECG	At least 10 minutes in supine position prior to recording
		AE/SAE recording	If the screening visit is performed on two separate days, the AE/SAE questions will be asked again
		Inclusion/exclusion criteria	

Abbreviations: AE = adverse event; BMI = body mass index; mCC = menthol conventional cigarette(s); ECG = electrocardiogram; HIV = human immunodeficiency virus; SAE = serious adverse event; THS = tobacco heating system.

The sequence of assessments/events is given just for illustrative purpose. The sequence will be at the discretion of the site after signature of ICF.

9.2 Confinement Period (Days -2 to 6)

9.2.1 Admission (Day -2)

The procedures of Day -2 can be performed in order deemed most practical, except the product test which will be the last assessment prior to enrolment after all eligibility criteria have been met. Subjects will attend the investigational site in at least 10-hour fasting state for clinical laboratory to be assessed.

Table 8 shows the assessments that will be performed at Admission (Day -2):

Table 8. Time Schedule – Day -2

Time	Blood sample	Procedures	Additional information
Start of procedure		**Admission**	
		AE/SAE recording; Concomitant medication	All day
Time of admission-06:30 PM		Urine pregnancy test (all females only)	
Time of admission-06:30 PM		Advice on the risk of smoking and debriefing	
Time of admission-06:30 PM		Smoking history	
Time of admission-06:30 PM		Willingness to abstain from smoking for up to 90 days	
Time of admission-06:30 PM		Urine drug screen	
Time of admission-06:30 PM		Urine cotinine screening test	
Time of admission-06:30 PM		Alcohol breath test screen	
Time of admission-06:30 PM		CO breath test	Irrespective of the time of product use
Time of admission-06:30 PM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
Time of admission-06:30 PM		Physical examination, and weight, waist circumference, and BMI	Weight and waist circumference to be evaluated also as risk markers
Time of admission-06:30 PM		Inclusion/exclusion criteria	
Time of admission-06:30 PM		Identification of current mCC brand	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Admission**	
Time of admission-06:30 PM		Product test of THS 2.2 Menthol	Must be done only after the pregnancy test is confirmed negative. The product test is the last assessment prior to enrolment.
Time of admission-06:30 PM		Enrolment	After all inclusion and exclusion criteria have been satisfactorily met
		Preference product question	Has to be done after enrolment
Before 09:00 PM		Dinner	
11:00 PM		End of smoking period	

Abbreviations: AE = adverse event; BMI = body mass index; mCC = menthol conventional cigarette(s); CO = carbon monoxide; SAE = serious adverse event; THS = tobacco heating system.

9.2.2 Baseline Period (Day-1 06:30 AM to Day 1 06.29 AM)

Table 9 and Table 10 show the assessments that will be performed at baseline (Day -1 and Day 0, respectively):

Table 9. Time Schedule – Day -1

Time	Blood sample	Procedures	Additional information
Start of procedure		**Baseline Day -1**	
		AE/SAE questioning; Concomitant medication	All day
06:30 AM+/-20min		Start collection of 24-hour urine to Day -1 sampling bottle	The subject must empty his bladder and discard the urine prior o the start of urine collection
		CO breath test	Within 15 minutes before first mCC
06:30 AM		Beginning of smoking	
Before 10:00 AM		Breakfast	
Before 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
12:00 PM-01:30 PM		CO breath test	
Before 02:30 PM		Lunch	
04:00 PM-05:30 PM		CO breath test	
Afternoon		Snacks	
Evening until 09:00 PM		Dinner	
08:00 PM-09:30 PM		CO breath test	
08:00 PM-09:30 PM	√	COHb in blood	
08:00 PM-11:00 PM		MCEQ questionnaire QSU-brief questionnaire	
11:00 PM		End of smoking	
06:30 AM-11:15 PM		Collection of all smoked mCC butts	For accountability

Abbreviations: AE = adverse event; COHb = carboxyhemoglobin; mCC = menthol conventional cigarette(s); CO = carbon monoxide; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event.

Table 10. Time Schedule – Day 0

Time	Blood sample	Procedures	Additional information
Start of procedure		**Baseline Day 0**	
		AE/SAE questioning; Concomitant medication	All Day
		Randomization	At any time of the day after eligibility criteria have been met. Subjects are not to be informed of their assigned arm until Day 1
06:29 AM+/-20min		End of 24-hour urine collection andsamples to be taken from the 24-hour urine after the final portion of urine has been added to Day -1 sampling bottle.	BoExps (primary secondary and NEQ) and creatinine
06:30 AM+/-20min		Start collection of 24-hour urine to Day 0 sampling bottle	
	√	CYP2A6 activity in plasma	Has to be done prior to smoking
		Spirometry without short-acting bronchodilator	Has to be done prior to smoking
		Assessment of cough	Has to be done prior to smoking but no later than 10:00 AM
		MNWS questionnaire	Has to be done prior to smoking but no later than 10:00 AM
		CO breath test	Within 15 minutes before first smoking event.
06:30 AM to 11:00 PM		HST	HST SODIM® device has to be done for all product uses if compatible mCCs are smoked
06:30 AM		Beginning of smoking	
	√	Clinical laboratory parameters (hematology, clinical chemistry) and risk markers: hs-CRP, fibrinogen, homocysteine, LDL, HDL, HbA1c, sICAM-1	Has to be done after at least 10 hours of fasting. Blood glucose, TG, TC, WBC, platelet count from safety will be evaluated also as risk markers

Time	Blood sample	Procedures	Additional information
Start of procedure		**Baseline Day 0**	
	√	Blood sampling for bio-banking for transcriptomics	If consent is obtained Has to be done after at least 10 hours of fasting
	√	Bio-banking for BoExp/ risk markers in serum/plasma (if consent is obtained)	If consent is obtained Has to be done after at least 10 hours of fasting
		Urine safety analysis	
Before 10:00 AM		Breakfast	
Before 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement Systolic and diastolic BP to be evaluated also as risk markers
10:00 AM-11:30 AM		A caffeine tablet containing approximately 170 mg of caffeine + 150 ml water ± 10 ml	The time of the tablet intake must be recorded
12:00 PM-01:30 PM		CO breath test	
Before 02:30 PM		Lunch	
04:00 PM-05:30 PM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the caffeine tablet
04:00 PM-05:30 PM		CO breath test	
Afternoon		Snacks	
Before 09:00 PM		Dinner	
08:00 PM-09:30 PM		CO breath test	
08:00 PM-09:30 PM	√	COHb in blood	
08:00 PM-09:30 PM	√	Nicotine, cotinine in plasma	
08:00PM-11:00 PM		HST questionnaire	If compatible mCC are smoked
08:00 PM-11:00 PM		MCEQ questionnaire, QSU-brief questionnaire	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Baseline Day 0**	
11:00 PM		End of smoking	
06:30 AM-11:15 PM		Collection of all mCC butts	For accountability

Abbreviations: AE = adverse event; BoExps = biomarkers of exposure; BP = blood pressure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; HbA1c = hemoglobin A1c; hs-CRP = high-sensitive C-reactive protein; HDL = high density lipoprotein; HST = human smoking topography; LDL = low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; WBC = white blood cell count.

* Platelet count, WBC, blood glucose, triglycerides, and total cholesterol from safety will also be assessed as risk markers

9.2.3 Exposure Period in Confinement (Days 1 06: 30 AM to time of Discharge on Day 6)

The tables in this Section show the assessments that will be performed during the confinement period (Day 1 to Day 5). Table 11 shows the assessments that will be performed on Day 1:

Table 11. Time Schedule – Day 1

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 1**	
		AE/SAE questioning; Concomitant medication	All day
		Support for smoking abstinence (SA arm only) if needed	All day
Before 06:30 AM		Subjects are informed of their assigned study arm	
06:29 AM+/-20min		End of 24-hour urine collection and samples to be taken from the 24-hour urine after final portion of urine has been added to Day 0 sampling bottle.	BoExps (primary, secondary and NEQ), creatinine, and Ames mutagenicity in 24-hour urine Risk markers: 11-DTX-B2, 8-epi-PGF2α, Bio-banking for BoExp/ risk markers (if additional consent is obtained)

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 1**	
			Must be prior to first product use of Day 1
06:30 AM+/-20min		Start collection to Day 1 sampling bottle 24-hour urine	
		Assessment of cough (VAS)	To be done prior to product use but no later tha 10:00 PM
		MNWS questionnaire	To be done prior to product use but no later tha 10:00 PM
		CO breath test	Within 15 minutes before first product use (for THS 2.2 Menthol and mCC arms) or between 08:00 AM-09:30 AM (SA arm)
06:30 AM-11:00 PM		HST	In THS 2.2 Menthol and mCC arms, it should be done for all smoking events with HST SODIM® device, if compatible mCCs are smoked
06:30 AM		Beginning of product use	
Before 10:00 AM		Breakfast	
10:00 AM-11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
12:00 PM-01:30 PM		CO breath test	
Before 02:30 PM		Lunch	
04:00 PM-05:30 PM		CO breath test	
Afternoon		Snacks	
In the evening before 09:00 PM		Dinner	
08:00 PM-09:30 PM		CO breath test	
08:00 PM-09:30 PM	√	COHb in blood	
08:00 PM-09:30 PM	√	Nicotine, cotinine in plasma	
08:00PM-11:00 PM		MCEQ questionnaire (THS 2.2 Menthol and mCC arms only), QSU-brief questionnaire	
11:00 PM		End of product use	
6:30 AM-11:15 PM		Collection of used mCC butts	For accountability

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 1**	
6:30 AM-11:15 PM		Collection of all tobacco plugs and filters from Menthol Tobacco Sticks	For accountability and further analysis

Abbreviations: AE = adverse event; BoExps = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; CoHb = carboxyhemoglobin; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event; THS = tobacco heating system.

Table 12 shows the assessments that will be performed on Day 2 of the confinement period:

Table 12. Time Schedule – Day 2

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 2**	
		AE/SAE questioning; Concomitant medication	All day
		Support during smoking abstinence (SA arm only) if needed	All day
6:29 AM+/-20min		End of 24-hour urine collection andsamples to be taken from the 24-hour urine after the final portion of urine has been added to Day 1 sampling bottle.	BoExps (primary, secondary, and NEQ) and creatinine
6:30 AM+/-20min		Start collection to Day 2 sampling bottle 24-hour urine	
		Assessment of cough	To be done prior to product use but no later than 10:00 AM
		MNWS questionnaire	To be done prior to product use but no later than 10:00 AM
		CO breath test	Within 15 minutes before first product use (for THS 2.2 Menthol and mCC arms) or between 08:00 AM-09:30 AM (SA arm)
6:30 AM		Beginning of product use	
Before 10:00 AM		Breakfast	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 2**	
Before 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
12:00 PM-01:30 PM		CO breath test	
Before02:30 PM		Lunch	
04:00 PM-05.30 PM		CO breath test	
Afternoon		Snacks	
In the evening before 09:00 PM		Dinner	
08:00 PM-09:30 PM		CO breath test	
08:00 PM-09:30 PM	√	COHb in blood	
08:00 PM-09:30 PM	√	Nicotine, cotinine in plasma	
08:00 PM-11:00 PM		MCEQ questionnaire (THS 2.2 Menthol and mCC arms only), QSU-brief questionnaire	
11:00 PM		End of product use	
6:30 AM 11:15 PM		Collection of used mCC butts	For accountability
6:30 AM 11:15 PM		Collection of all tobacco plugs and filters from Menthol Tobacco Sticks	For accountability and further analysis

Abbreviations: AE = adverse event; BoExps = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; CoHb = carboxyhemoglobin; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event; THS = tobacco heating system.

Table 13 shows the assessments that will be performed on Day 3 of the confinement period:

Table 13. Time Schedule – Day 3

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 3**	
		AE/SAE questioning; Concomitant medication	All day
		Support during smoking abstinence (SA arm only) if needed	All day
6:29 AM+/-20min		End of 24-hour urine collection and samples to be taken after final portion of urine has been added to Day 2 sampling bottle	BoExps (primary, secondary, and NEQ)and creatinine
6:30 AM+/-20min		Start collection to Day 3 sampling bottle 24-hour urine	
		MNWS questionnaire	To be done prior to product use but no later than 10:00 AM
		Assessment of cough	To be done prior to product use but no later than 10:00 AM
		CO breath test	Within 15 minutes before first product use for THS 2.2 Menthol and mCC arms or between 08:00 AM-09:30 AM (SA arm)
6:30 AM		Beginning of product use	
Before 10:00 AM		Breakfast	
10:00 AM-11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
12:00 PM-01:30 PM		CO breath test	
Before 02:30 PM		Lunch	
04:00 PM-05:30 PM		CO breath test	
Afternoon		Snacks	
In the evening before 09:00 PM		Dinner	
08:00 PM-09:30		CO breath test	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 3**	
PM			
08:00 PM-09:30 PM	√	COHb in blood	
08:00 PM-09:30 PM	√	Nicotine, cotinine in plasma	
08:00 PM-11:00 PM		MCEQ questionnaire (THS 2.2 Menthol and mCC arms only), QSU-brief questionnaire	
11:00 PM		End of product use	
6:30 AM-11:15 PM		Collection of used mCC butts	For accountability
6:30 AM-11:15 PM		Collection of all tobacco plugs and filters from Menthol Tobacco Sticks	For accountability and further analysis

Abbreviations: AE = adverse event; BoExps = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; CoHb = carboxyhemoglobin; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event; THS = tobacco heating system.

Table 14 shows the assessments that will be performed on Day 4 of the confinement period:

Table 14. Time Schedule – Day 4

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 4**	
		AE/SAE questioning; Concomitant medication	All day
		Support during smoking abstinence (SA arm only) if needed	All day
		Socio-economic status questionnaire	At any time of the day
6:29 AM+/-20min		End of 24-hour urine collection andsamples to be taken from 24-hour urine after final portion of urine has been added to Day 3 sampling bottle.	BoExps (primary, secondary, and NEQ) and creatinine
6:30 AM+/-20min		Start collection to Day 4 sampling bottle 24-hour urine	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 4**	
		Assessment of cough	To be done prior to product use but no later than 10:00 AM.
		MNWS questionnaire	To be done prior to product use but no later than 10:00 AM.
		CO breath test	Within 15 minutes before first product use for THS 2.2 Menthol and mCC arms) or between 08:00 AM-09:30 AM (SA arm)
06:30 AM-11:00 PM		HST	In THS 2.2 Menthol and mCC arms, HST SODIM® device has to be used for all product use if compatible mCCs are smoked
6:30 AM		Beginning of product use	
Before 10:00 AM		Breakfast	
Before 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
12:00 PM-01:30 PM		CO breath test	
Before 02:30 PM		Lunch	
04:00 PM-05:30 PM		CO breath test	
Afternoon		Snacks	
In the evening before 09:00 PM		Dinner	
08:00 PM-09:30 PM		CO breath test	
08:00 PM-09:30 PM	√	COHb in blood	
08:00 PM-09:30	√	Nicotine, cotinine in plasma	
08:00 PM-09:30		HST questionnaire for all subjects in the THS 2.2 Menthol and mCC arms	If compatible mCC are smoked
08:00 PM-11:00 PM		MCEQ questionnaire (THS 2.2 Menthol and mCC arms only),	
		QSU-brief questionnaire	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 4**	
11:00 PM		End of product use	
6:30 AM-11:15 PM		Collection of used mCC butts	For accountability
6:30 AM-11:15 PM		Collection of tobacco plugs and filters from all Menthol Tobacco Sticks butts	For accountability and further analysis

Abbreviations: AE = adverse event; BoExps = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; CoHb = carboxyhemoglobin; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event; THS = tobacco heating system.

Table 15 shows the assessments that will be performed on Day 5 of the confinement period:

Table 15. Time Schedule – Day 5

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 5**	
		AE/SAE questioning; Concomitant medication	All day
		Support during smoking abstinence (SA arm only) if needed	All day
6:29 AM+/-20min		End of 24-hour urine collection and samples to be taken from 24-hour after final portion of urine has been added to Day 4 sampling bottle.	BoExps (primary secondary and NEQ) and creatinine
6:30 AM+/-20min		Start collection to Day 5 sampling bottle 24-hour urine	
		Assessment of cough	To be done prior to product use but no later than 10:00 AM.
		MNWS questionnaire	To be done prior to product use but no later than 10:00 AM.
		CO breath test	Within 15 minutes before first product use for THS 2.2 Menthol and mCC arms) or between 08:00 AM-09:30 AM (SA arm)
	√	COHb in blood	Within 15 minutes before first product use for THS 2.2 Menthol and mCC arms) or between 08:00 AM-09:30 AM (SA arm)

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 5**	
	√	Nicotine, cotinine in plasma	For THS 2.2 Menthol and mCC arms: within 15 minutes before first product use (T_0): then additional blood samples at 2 hour intervals from T_0 until 11:00 PM. Each sample has a time window of +5 minutes For SA arm:only one blood sampling betweent 08:00 PM-09:30 PM
6:30 AM		Beginning of product use	
Before 10:00 AM		Breakfast	
Before 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement
10:00 AM-11:30 AM		A caffeine tablet containing around 170 mg of caffeine + 150 ml water ± 10 ml	The time of the tablet intake must be recorded
12:00 PM-01:30 PM		CO breath test	
12:00 PM-01:30 PM	√	COHb in blood	
Before 02:30 PM		Lunch	
04:00 PM-05:30 PM		CO breath test	
04:00 PM-05:30 PM	√	COHb in blood	
04:00 PM-05:30 PM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the caffeine tablet
Aftenoon		Snacks	
In the evening before 09:00 PM		Dinner	
08:00 PM-09:30 PM		CO breath test	
08:00 PM-09:30 PM	√	COHb in blood	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 5**	
08:00 PM-11:00 PM		MCEQ questionnaire (THS 2.2 Menthol and mCC arms only), QSU-brief questionnaire	
11:00 PM		End of product use	
6:30 AM-11:15 PM		Collection of used mCC butts	For accountability
6:30 AM-11:15 PM		Collection of tobacco plugs and filters from Menthol Tobacco Sticks	For accountability and frutrher analysis

Abbreviations: AE = adverse event; BoExps = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme;; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; THS = tobacco heating system; WBC = white blood cell count.

Table 16 shows the assessments that will be performed on Day 6, prior to Discharge from the study unit:

Table 16. Time Schedule – Day 6

Time	Blood sample	Procedure	Additional information
Start of procedure		**Day of Discharge Day 6**	
		AE/SAE recording; Concomitant medication	All day until discharge
		Support during smoking abstinence (SA arm only) if needed	All day until discharge
	√	Nicotine, cotinine - blood sampling: PK	In THS 2.2 Menthol and mCC arms, 20 and 24 hours blood sampling after T0 of Day 5. Each sample has a time window of ±5 minutes In SA arm, one blood sample will be drawn between 08:00 AM-09:30 AMmin

Time	Blood sample	Procedure	Additional information
Start of procedure		**Day of Discharge Day 6**	
6:29 AM+/-20min		End of 24-hour urine collection and samples to be taken from the 24-hour urine after final portion of urine has been added to Day 5 sampling bottle	BoExps (primary, secondary, and NEQ) and creatinine, and Ames mutagenicity Risk markers: 11-DTX-B2, 8-epi-PGF2α, Biobanking for BoExp/risk markers (if consent is obtained)
	√	CYP2A6 activity in plasma	Has to be done prior to product use
		Assessment of cough	To be done prior to product use but no late.r than 10:00 AM
		MNWS questionnaire	To be done prior to product use but no late.r than 10:00 AM
		Spirometry without short-acting bronchodilator	Has to be done prior to product use
6:30 AM		Beginning of product use	
	√	Clinical laboratory parameters (hematology, clinical chemistry)*, risk markers: sICAM-1	Has to be done after at least 10 hours of fasting. *platelet count, and WBC to be evaluated also as risk marker
	√	Bio-banking for BoExp/ risk markers in serum/plasma (if consent is obtained)	Has to be done after at least 10 hours of fasting
	√	Bio-banking for transcriptomics (if consent is obtained)	Has to be done after at least 10 hours of fasting
Before 09:00 AM		Breakfast	
Prior to discharge of Day 6		Physical examination, and weight and calculated BMI	
Prior to discharge of Day 6		CO breath test	
Prior to discharge of Day 6		Urine safety analysis	

Time	Blood sample	Procedure	Additional information
Start of procedure		**Day of Discharge Day 6**	
Prior to discharge of Day 6		Urine pregnancy test (all females only)	
Prior to discharge of Day 6		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement Systolic and diastolic BP to be evaluated also as risk marker
Prior to discharge of Day 6		ECG	At least 10 minutes in supine position prior to recording
Prior to discharge of Day 6		Distribution of product use electronic diary	To be completed by the subject every day from time of Discharge on Day 6 until next visit. All Menthol Tobacco Sticks/mCC and any tobacco/nicotine containing products have to be recorded.
Prior to discharge of Day 6		Advice on risk of smoking and debriefing	
Prior to discharge of Day 6		Collection of all used Menthol Tobacco Sticks and smoked mCC butts	For accountability
Prior to discharge of Day 6		Time of Discharge from confinement/- beginning of the exposure ambulatory period	

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; BMI = body mass index; BoExps = biomarkers of exposure; BP = blood pressure; mCC = conventional cigarette(s); CO = carbon monoxide; CYP = cytochrome P450 enzyme; ECG = electrocardiogram; MNWS = Minnesota Nicotine Withdrawal Scale; PK = pharmacokinetics; SA = smoking abstinence; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; WBC = white blood cell count.

9.3 Ambulatory Period (from time of Discharge on Day 6 to time of Discharge of Day 90 Visit on Day 91)

For Day 30 Visit, and Day 60 Visit, a time window of +/- 3 days will be allowed with respect to Day 30 and Day 60 respectively. The time of opening and end of the visit are given as an estimate.

Table 17 shows the assessments that will be performed on Day 30 and Day 60 of the ambulatory period:

Table 17. Time Schedule – Day 30 Visit (from 08:00 AM on Day 30 to check-out of the subject on Day 31) and Day 60 Visit (from 08:00 AM to check out of the subject on Day 61)

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 30 and Day 60**	
08:00 AM		Opening of the Day 30 and Day 60 Visits	No product restriction prior to the opening of the visit Product use will be allowed on site in the THS 2.2 Menthol and mCC arms from 08:00 AM to 11:00 PM The use of THS 2.2 menthol in smokers allocated to mCC and SA arms will be forbidden
		Support for smoking cessation (SA arm only) if needed	At any time of the day
		AE/SAE questioning; Concomitant medication	At any time during the day
08:30 AM-09:30 AM		Start of HST recording for 4 hours	In the THS 2.2 Menthol and mCC arms, the HST SODIM® device has to be used for all smoking events, if compatible mCCs are smoked HST recording will be done only with the assigned product of the subject
09:00 AM ± 20 min		Start of 24-hour urine collection to Day 30 and Day 60 sampling bottles	The subject must empty his bladder and discard the urine prior to starting urine collection
Before 10:00 AM		Breakfast	
10:00 AM-11:30 AM		CO breath test	Irrespective of the time of product use
10.00 AM-11:30 AM	√	COHb in blood	Irrespective of the time of product use
10.00 AM-11:30 AM	√	Nicotine, cotinine in plasma	One blood sample will be drawn, irrespective of the time of product use

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 30 and Day 60**	
12:30 PM-01:30 PM		End of HST recording	The HST should be recorded over a period of 4 hours ± 15 minutes. HST recording will be done only on the subject's assigned product
Before 02.30 PM		Lunch	
02:30 PM -07:00 PM		ECG	At least 10 minutes in supine position prior to recording
02:30 PM -07:00 PM		Physical examination, including weight calculated BMI,	
02:30 PM -07:00 PM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement Systolic and diastolic BP to be evaluated also as risk markers
08:00 PM-09:30 PM		HST questionnaire (THS 2.2 Menthol and mCC arms only)	If compatible mCC are smoked
08:00 PM-11:00 PM		MCEQ questionnaire (THS 2.2 Menthol and mCC arms only), QSU-brief questionnaire	
In the evening before 09:00 PM		Dinner	
11:00 PM		End of Product use	
08:00 AM-11:15 PM		Collection of empty/partially used Menthol Tobacco Stick packs	For accountability Partially used packs will be returned to the subject
08:00 AM-11:15 PM		Collection of tobacco plugs from each used Menthol Tobacco Sticks	For further analysis

Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; BoExps = biomarkers of exposure; CO = carbon monoxide; COHb = carboxyhemoglobin; HDL: high density lipoprotein; ; hs CRP: high sensitive C-reactive protein; HST = human smoking topography; LDL: low density lipoprotein; mCC = menthol conventional cigarette(s); MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; SAE = serious adverse event; s-ICAM-1: soluble inter-cellular Molecule 1; TC: total cholesterol; TG = triglycerides; THS = tobacco heating system; QSU = Questionnaire of Smoking Urges; WBC = white blood cell count.

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 31 and Day 61**	
		Support for smoking cessation (SA arm only) if needed	At any time of the day
		AE/SAE questioning; Concomitant medication	At any time during the day
	√	Clinical laboratory parameters (hematology, clinical chemistry) *, and risk markers (s-ICAM-1, hs-CRP, fibrinogen, homocysteine, LDL, HDL,)	Sample to be collected after at least 10 hours of fasting. *Blood glucose, TG, TC, WBC, and platelet count from safety lab will be also evaluated as risk markers
06:30 AM		Beginning of product use	
08:59 PM ± 20 min		End of urine collection and urine sample to be taken from the 24-hour urine after final portion of urine has been added to Day 30 or Day 60 sampling bottles	BoExp (primary, secondary, and NEQ), creatinine Risk markers: 11-DTX-B2 and 8-epi-PGF2α
Before 10:00 AM		Assessment of Cough MNWS questionnaire	Irrespective of the time of product use but no later than 10:00 AM
Before 10:00 AM		Breakfast	
Prior to check.out of the given visit		Urine safety analysis and pregnancy test	
Prior to check.out of the given visit		Advice on the risk of smoking and debriefing	
Check-out		End of the Visit	

Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; BoExps = biomarkers of exposure; CO = carbon monoxide; COHb = carboxyhemoglobin; HDL: high density lipoprotein; ; hs CRP: high sensitive C_reactive protein; HST = human smoking topography; LDL: low density lipoprotein; mCC = menthol conventional cigarette(s); MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; SAE = serious adverse event; s-ICAM-1: soluble inter-cellular Molecule 1; TC: total cholesterol; TG = triglycerides; THS = tobacco heating system; QSU = Questionnaire of Smoking Urges; WBC = white blood cell count.

The procedures for the last visit which will be conducted on Day 90 Visit +/- 3 days of the study are shown in Table 18.

The time of opening and end of the visit are given as an estimate.

Table 18. Time Schedule – Day 90 Visit (08:00 AM of Day 90 to time of discharge of Day 91)

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 90**	
08.00 AM		Opening of the Visit	No product restriction prior to the opening of the visit Product use will be allowed on site in the THS 2.2 Menthol and mCC arms from 08:00 AM to 11:00 PM The use of THS 2.2 Menthol in smokers allocated to mCC and SA arms will be forbidden
		AE/SAE questioning; Concomitant medication	At any time during the day
		Support for smoking cessation (SA arm only) if needed	At any time of the day
08:30 AM-09:30 AM		Start of HST recording for 4 hours	In the THS 2.2 Menthol and mCC arms, the HST SODIM® device has to be used for all smoking events, if compatible mCCs are smoked HST recording will be done only on the subject's assigned product
09:00 AM ± 20 min		Start of collection of 24-hour urine to Day 90 sampling bottle	The subject must empty his bladder and discard the urine prior to starting urine collection
Before 10:00 AM		Breakfast with a caffeine tablet containing approximately 170 mg of caffeine + 150 ml water ± 10 ml	The time of the tablet intake must be recorded
10:00 AM-12:30 PM		CO breath test	Irrespective of the time of product use
10:00 AM-12:30 PM	√	COHb in blood	Irrespective of the time of product use
10:00 AM-12:30 PM	√	Nicotine, cotinine in plasma	One blood sample will be drawn, irrespective of the time of product use
12:30 PM-01:30 PM		End of collection HST recording	The HST should be recorded over a period of 4 hours ± 15 minutes
Before 02:30 PM		Lunch	

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 90**	
03:00 PM-04:00 PM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the caffeine tablet
08:00 PM-09:30 PM		HST questionnaire (THS 2.2 Menthol and mCC arms only)	If compatible mCC are smoked
08:00 PM-11:00 PM		Fagerström Test for Nicotine Dependence (FTND)	
08:00 PM-11:00 PM		MCEQ (THS 2.2 Menthol and mCC arms, only)	
08:00 PM-11:00 PM		QSU-brief questionnaire	
In the evening before 09:00 PM		Dinner	
08:00 AM-11:15 PM		Collection of empty/partially used menthol THS tobacco stick packs	At any time of the day For accountability Partially used packs will be returned to the subject
08:00 AM-11:15 PM		Collection of tobacco plugs from each used Menthol Tobacco Stick	All day For further analysis

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event;; BMI = body mass index; BoExps = biomarkers of exposure; mCC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; ECG = electrocardiogram; HbA1c = hemoglobin A1c; hs-CRP = high-sensitive C-reactive protein; HDL = high density lipoprotein; HST = human smoking topography; LDL = low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; TG = triglycerides; THS = tobacco heating system; WBC = white blood cell count.

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 91**	
		AE/SAE questioning; Concomitant medication	At any time during the day
	√	CYP2A6 activity in plasma	Has to be done prior to smoking

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 91**	
		Assessment of cough	To be done no later than 10:00 AM Has to be done prior to smoking
		MNWS questionnaire	To be done no later than 10:00 AM Has to be done prior to smoking
		Spirometry without short-acting bronchodilator	Has to be done prior to smoking
08:59 PM ± 20 min		End of urine collection and urine sample to be taken from the 24-hour urine after final portion of urine has been added to Day 90 sampling bottle	BoExp (primary, secondary, and NEQ), creatinine, ames mutagenicity Urine biobanking Risk markers: 11-DTX-B2 and 8-epi-PGF2α
	√	Clinical laboratory parameters (hematology, clinical chemistry)*, and risk markers (s-ICAM-1, hs-CRP, fibrinogen, homocysteine, LDL, HDL, TG, HbA1c)	Sample to be collected after at least 10 hours of fasting. *Blood glucose, TG, TC, WBC, and platelet count from safety to be evaluated also as risk markers
	√	Bio-banking for transcriptomics	Sample to be collected after at least 10 hours of fasting If consent is obtained
	√	Bio-banking for BoExp/risk markers in serum/plasma	Sample to be collected after at least 10 hours of fasting If consent is obtained
Before10:00AM		Breakfast	
In the afternoon prior to discharge of Day 91		Physical examination, including weight calculated BMI, and waist circumference	Weight and waist circumference to be evaluated also as risk markers

Time	Blood sample	Procedures	Additional information
Start of procedure		**Day 91**	
In the afternoon prior to discharge of Day 91		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position prior to measurement At any time during the day Systolic and diastolic BP to be evaluated also as risk marker
In the afternoon prior to discharge of Day 91t		ECG	At least 10 minutes in supine position prior to recording
In the afternoon prior to discharge of Day 91		Urine safety analysis and pregnancy test	
In the afternoon prior to discharge of Day 91		Advice on the risk of smoking and debriefing	
		Time of Discharge On Day 91	

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event;; BMI = body mass index; BoExps = biomarkers of exposure; mCC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; ECG = electrocardiogram; HbA1c = hemoglobin A1c; hs-CRP = high-sensitive C-reactive protein; HDL = high density lipoprotein; HST = human smoking topography; LDL = low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; TG = triglycerides; THS = tobacco heating system; WBC = white blood cell count.

9.4 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 subjects have completed the Day 91 safety assessments (or if they are prematurely withdrawn from the study), they will enter a 28-day safety follow-up period.

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

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

9.5 Early Termination Procedures

The safety assessments as described on Day 6 will be performed as early termination procedures (see Section 9.2.4).

10 CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

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

The Principal Investigator/head of the investigational site shall permit the Monitor to review study data as frequently as considered necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor in order 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 done and documented.

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

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

Communication by telephone, mail, and e-mail may be used as needed to supplement site visits. The Investigator and study collaborator 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 study collaborator 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 study collaborator 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 Study Collaborators

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 meeting, the PI will ensure that appropriate training relevant to the study is provided to all study collaborator involved in the study, and that any new information relevant to the performance of this study is forwarded to the study collaborator involved in a timely manner. The record of all individuals involved in the study will be maintained in the Site Investigator File.

10.3 Audits and Inspections

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

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. The Principal Investigator/head of investigational site 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 collaborator 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 authorized designee 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 on paper copy. Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol in the source documents and then transferring the data into the eCRF according to the eCRF Completion Guidelines.

The Principal 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 CRA. 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.

For the ePRO device, all subject reported outcome data will be provided in English and instructions will be provided in the subject's local language.

11.1.2 Protocol Deviations

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 CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the start of the study. This document will describe, in detail, the Data Management related procedures and processes.

All data of all subjects enrolled and screening failures who experience an AE during the study (from time of informed consent to 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 DMP and Data Validation Specifications. Discrepancies will be reported as defined in DMP and Data Validation Plan.

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 Menthol device issues and/or malfunctions:	C54451/Medical_Device_Problem_Codes_FDA_CDRH

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 the data is reviewed by the Sponsor, resolution of all raised queries and QC of the changed data, database, or selected data upon Sponsor approval as applicable, is declared locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the Data Management and Statistical 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 DMP in Clinical Data Interchange Standards Consortium's Study Data Tabulation Model (SDTM) Data Structure Specifications.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis will be given in a Statistical Analysis Plan (SAP). Any changes to the planned statistical methods will be documented in the Clinical Study Report. The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

For the primary analysis of the BoExp, the following stratification criteria will be used:

1. Sex (male; female).
2. Average daily CC consumption over the last 4 weeks as reported during the Screening.

12.1.2 Definitions for Statistical Data Analysis

Baseline:

In general, baseline will be the last available time-point prior to Day 1, 06:30 AM.

THS 2.2 Menthol users:Subjects switching from mCC to THS 2.2 Menthol whose product use pattern categorization is primarily THS 2.2 Menthol or predominantly THS 2.2 Menthol over a defined period will be considered as THS 2.2 Menthol users during that period.. See Section 12.3 for further details on the product use.

Dual use:

Subjects switching from mCC to THS 2.2 Menthol whose product use pattern categorization is dual mostly THS 2.2 Menthol, dual balanced or dual mostly CC over a defined period will be considered as dual users. See Section 12.3 for further details on the product use.

CC users:

Subjects switching from mCC to THS 2.2 Menthol or subjects continuing to use mCC whose product use pattern categorization is primarily CC or predominantly CC over a defined period will be considered as CC users during that period. See Section 12.3 for further details on the product use.

Smoking abstinence:

Smoking abstinence during a defined period is defined as using no tobacco-containing product as reported by the subject on the electronic diary.

12.1.3 Descriptive Statistics

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

Descriptive statistics for continuous variables (number of subjects [n], number and percent of subjects with 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 be presented by product arm and overall at each time point, where applicable.

For BoExp, the geometric mean and coefficient of variation will be presented in addition to the mean and standard deviation.

Analyses over time will be descriptive statistics of parameters at each assessment timepoint.

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

Missing values for the BoExp will be imputed using the last observation carried forward (LOCF) approach.

Values below the lower limit of quantification (LLOQ) will be imputed using 0.5 x LLOQ. For values above the upper limit of quantification (ULOQ), the ULOQ 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.

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.

12.1.5 Significance Level for Inferential Analysis

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

The primary endpoints will be tested using a multiple testing procedure to preserve the overall alpha level by simultaneously testing the endpoints using a closed procedure with each test performed at an alpha level of 5%. This implies that statistical significance is required for all primary endpoints in order to be able to make confirmatory claims about any of the endpoints.

Further details will be provided in the SAP.

12.2 Determination of Sample Size and Power Consideration

The following discussion addresses the ability to demonstrate on Day 5 a reduction of at least 50% on four selected primary BoExps and on Day 90 on a fifth primary BoExp in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Table 19 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 Menthol and the two control arms in COHb, 3-HPMA, MHBMA and S-PMA on Day 5 based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study to investigate exposure to selected smoke constituents in smokers switching from conventional cigarettes to SMAR cigarettes for 5 days, the (YVD-CS01-EU study (ClinicalTrials.gov: ID: NCT00812279) sponsored by PMI. The mean ratios and coefficients of variations for SMAR/CC are expected to be the same as THS 2.2 Menthol/mCC.

Table 19. Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC

	THS 2.2 Menthol /mCC MR (CV)	THS 2.2 Menthol /SA MR (CV)
COHb	0.40 (0.32)	2.10 (0.20)
3-HPMA	0.30 (0.50)	1.70 (0.33)
MHBMA	0.15 (0.70)	1.00 (0.35)
S-PMA	0.20 (0.70)	1.15 (0.42)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = conventional cigarettes; COHb = carboxyhemoglobin; CV = coefficients of variation; MHBMA = monohydroxybutenyl mercapyuric acid; MR = mean ratios; S-PMA = S-phenylmercapturic acid; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Table 20 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 Menthol and the the mCC control arm in Total NNAL on Day 90 based on data from a a Philip Morris USA-sponsored randomized, controlled, switching, open-label, parallel-group, single-center study in 90 male and female adult smokers evaluated six biomarkers of tobacco smoke exposure over a 12-week period (Frost-Pineda et al., 2008). The mean ratios and coefficients of variations for EHCJLI /CC are expected to be the same as THS 2.2 Menthol/mCC.

Table 20. Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC

	THS 2.2 Menthol /mCC MR (CV)
Total NNAL	0.30 (0.60)

Abbreviations: Total NNAL = total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; MR = mean ratios; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Table 21 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 Menthol and the mCC control arm in COHb, 3-HPMA, MHBMA and S-PMA based on data from a single-center, open-label, randomized, controlled, 2-arm parallel group study to evaluate the exposure to selected smoke constituents in smoking, healthy subjects switching from conventional cigarettes to THS 2.1 compared to subjects continuing to smoke CC for 5 days, the ZRHX-EX-01 study (ClinicalTrials.gov: ID: NCT01780714) sponsored by PMI. The mean ratios and coefficients of variations for THS 2.1/CC are expected to be the same as THS 2.2 Menthol/mCC.

Table 21. Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC

	THS 2.2 Menthol /mCC MR (CV)
COHb	0.44 (0.14)
3-HPMA	0.28 (0.20)
MHBMA	0.11 (0.47)
S-PMA	0.07 (0.50)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = conventional cigarettes; COHb = carboxyhemoglobin; CV = coefficients of variation; MHBMA = monohydroxybutenyl mercapyuric acid; MR = mean ratios; S-PMA = S-phenylmercapturic acid; THS 2.2 = Tobacco Heating System 2.2.

Based on these two sets of assumptions on the mean ratios and coefficients of variations for the four primary BoExp on day 5, the power to demonstrate a reduction was computed.

The comparison will be run on the per protocol population as defined in Section12.4.2.

Subjects are expected not to have any reason for exclusion from the per protocol population in the confinement period for THS 2.2 Menthol arm and in ambulatory and confinement condition for the mCC arm.

50% of the subjects are expected to be excluded from the per protocol population in the THS 2.2 Menthol arm in the ambulatory (mostly due to lack of compliance to the randomized product). Thus the expected populations on which the reductions will be assessed as described in Table 22.

Table 22. Sample Size to Assess the Reductions

	Sample size to assess the reduction (THS 2.2 Menthol:/mCC)
COHb	80:40
3-HPMA	80:40
MHBMA	80:40
S-PMA	80:40
Total NNAL	40:40

Table 23 describes the expected power to demonstrate a reduction on all 5 primary BoExps in smokers switching from CC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and ZRHX-EX-01 given a sample size of 160 smokers (~80 in THS 2.2, ~40 in CC, and ~40 in the SA arm). Therefore subjects will be enrolled into the study until there are 160 smokers in the FAS population.

Table 23. Expected power (YVD-CS01-EU and ZRHX-EX-01 studies assumptions)

	Reduction					
Assumptions	50%	51%	52%	53%	54%	55%
YVD-CS01-EU	94%	88%	81%	70%	56%	38%
ZRHX-EX-01	98%	97%	92%	76%	41%	6%

Power considerations related to secondary endpoints of biological changes:

The sample size is sufficient to obtain 95% confidence intervals for the ratio between (geometrical) mean levels of primary BoExps in THS 2.2 Menthol and SA with upper and

lower limits deviating not more than 18% from the point estimates, with an 80% overall probability of achieving the desired precision of estimating the true mean.

This study has 80% power using a one-sided test with 2.5% type I error probability:

- To detect a 0.631 [mL/min/kg] (29%) difference between THS 2.2 Menthol and mCC in CYP1A2 activity, as measured by the caffeine clearance, assuming a standard deviation of 0.564. Effect size and variability are derived from data obtained in the (YVD-CS01-EU study sponsored by PMI.
- To detect a 24.71 [ng/g creatinine] (20%) difference between THS 2.2 Menthol and mCC in 11-DTX-B2, assuming a standard deviation of 43.78, as reported by Saareks et al., 2001. The anticipated effect size of THS 2.2 Menthol is assumed to be about 90% of the effect of smoking cessation reported in the paper by Saareks et al., 2001.

12.3 Product use

The FDA Draft Guidance on Modified Risk Tobacco Product Applications Draft (Section VI-A-2) (FDA, 2012a), FDA requires that an MRTP Application should contain scientific evidence about the effect the product may have on tobacco use behavior among current tobacco users including consideration of areas such as the expected rates of use of the tobacco product by current tobacco users and the use of the tobacco product in conjunction with other tobacco products.

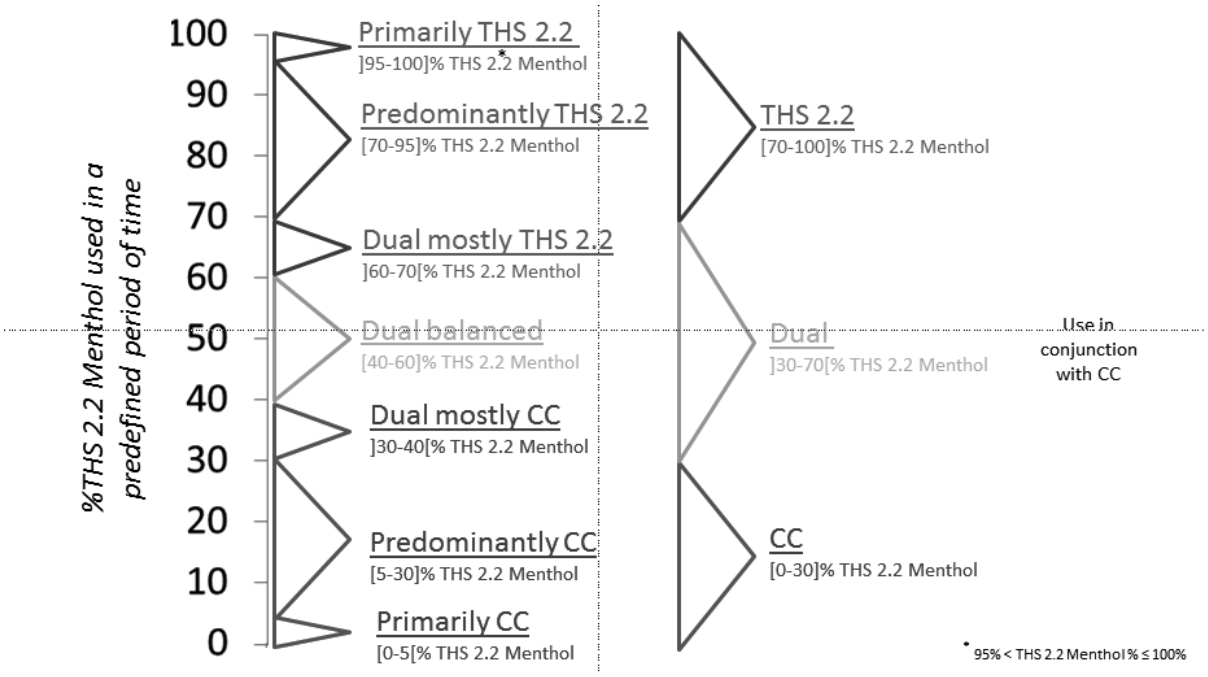
Although subjects being requested to use solely the product allocated to their respective study arm it is considered that during the ambulatory period not all subjects randomized to the THS2.2 Menthol arm might be exclusively using THS2.2 Menthol at all times during the study. Subjects may concomitantly use THS 2.2 Menthol and CC (dual-use). To assess dual use of THS 2.2 Menthol and CC, PMI has defined dual-use with regards to using THS 2.2 Menthol in the following way:

Dual-use will be calculated as percentage based on their reported THS 2.2 Menthol Tobacco Sticks consumption and the number of conventional cigarettes smoked (menthol and non-menthol) by study period:

- on Day 30, using the reported number of cigarettes and/or Menthol Tobacco Sticks consumption since time of Discharge,
- on Day 60, using the reported number of cigarettes and/or Menthol Tobacco Sticks consumption after Day 30 and
- on Day 90, using the reported number of cigarettes and/or Menthol Tobacco Sticks consumption after Day 60.

Figure 2 presents a detailed overview on the definition of the product use categories:

Figure 2 - Product Use Pattern Categorization



The more granular categorization scheme will be used for the definition of the per-protocol population and for the description of the product use patterns observed in the study whereas the less granular scheme will be used for the presentation of other study endpoints (e.g. safety endpoints) to better understand the impact of product.

As the calculation of the sample size was based on the primary objective (reduction of biomarkers levels in THS 2.2 Menthol relative to mCC), we assumed 50% of the subjects in the THS 2.2 Menthol arm would be using THS 2.2 Menthol exclusively and therefore will be included in the per-protocol population on Day 90.

In order to further optimize the assessment of BoExp and increase the comparability of the levels of BoExp between THS 2.2 Menthol and SA the confounding effects of the use of any other tobacco or nicotine containing product (other than the assigned product) need to be controlled for. Therefore a subject will be considered abstinent based on the following categorization:

- "Abstinence": 100% abstinence from tobacco or nicotine containing product use other than the assigned product

- Predominantly abstinent not more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average and no more than two uses on a single day occur.
- "Not abstinent": more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average or more than two uses on a single day occur.

The purpose of the defined threshold was to reduce the confounding effects of the use of any other tobacco or nicotine containing product (other than the assigned product). The results of a study PMI conducted in 2011 to evaluate the capacity of the urinary biomarker CEMA to detect smoking of small amounts of CC use (down to 2 CCs) per day was used to help us identify this threshold. The results of this study show that CEMA used as a urinary BoExp to acrylonitrile is able to discriminate between non-smokers and smokers who have smoked only 2 CCs and 4 CCs with a maximum level of sensitivity and specificity at an optimal threshold of the 2.56 µg/L (CEMA C_{max} in non-smokers) for CEMA and 3.76 µg/g for CEMA concentration adjusted to creatinine. For non-smokers CEMA and CEMA concentration adjusted to creatinine were greater than the LLOQ on only one occasion.

12.4 Analysis Population

The per-protocol (PP) population will be the primary analysis for BoExp, and risk markers. The FAS will be the primary analysis set for compliance to randomization arm, exposure and questionnaires. Exposure and questionnaires will be described by randomization arm and according to the product use (exclusive THS 2.2 Menthol, dual-use of THS 2.2. Menthol and mCC, mCC exclusive, SA) groups.

A sensitivity analysis will be run on the compliant population for the for BoExp and risk markers.

The primary population for the assessment of safety will be the safety population. To evaluate the robustness of the interpretation of safety and the study level safety conclusions an additional subset of the safety analyses will also be presented on the full safety population, as specified in Section12.6.5. Safety will be summarized and presented by randomization arm and according to product use (exclusive THS 2.2 Menthol, dual-use of THS 2.2 Menthol, Menthol and mCC, mCC exclusive, SA).

12.4.1 Full Analysis Set

The FAS consists of all the randomized subjects who had at least one post-randomization product use experience, if randomized to THS 2.2 Menthol or mCC, have at least one valid

non-safety assessment (THS 2.2 Menthol, mCC, SA arms). Subjects that were enrolled at the site that was terminated due to ICH/GCP uncompliance will be excluded from the FAS.

12.4.2 Per Protocol Population

The PP population is a subset of FAS and includes all randomized subjects who

- have had compliance to their randomized arm if randomized to THS 2.2 Menthol or SA arms. Non-compliance will be defined over a period (confinement period,]Day6-Day 30 Visit],]Day 30 Visit-Day 60 Visit],]Day 60 Visit-Day 90 Visit] and will be defined as having smoked than 3 CC during a single day in that period or having smoked on average over that period more that, not including 0.5 cigarettes per day.
- have not been misrandomized.
- and have no major protocol deviation (to be further described in the SAP).

12.4.3 Safety Population

The safety population consists of all the subjects who had at least one exposure to THS 2.2 Menthol (product test at Admission Day). Subjects in the safety population will be analyzed according to actual exposure. Although subjects that were enrolled at the site that was terminated due to ICH/GCP uncompliance will be excluded from the safety population, they will be summarized within the Full Safety Population (see Section 12.4.4).

12.4.4 Full Safety Population

The full safety population consists of all the subjects who had at least one exposure to THS 2.2 Menthol (product test at Admission Day). Subjects in the full safety population will be analyzed according to actual exposure.

12.4.5 Compliant Population

The compliant population will be a subset of the PP Population for subjects from the THS 2.2 Menthol arm who are exclusive THS 2.2 Menthol users or exclusive mCC users, as defined in Section 12.3 or for subjects from the mCC arm.

12.5 Primary Analysis

12.5.1 Primary Endpoint Analysis Variables

The primary endpoints are:

- COHb on Day 5

- MHBMA on Day 5
- 3-HPMA on Day 5
- S-PMA on Day 5
- Total NNAL on Day 90.

See Section 3.4.1.

Evaluation criterion:

The study will be considered successful, if the study demonstrates a 50% reduction or more for all five primary BoExps in the THS 2.2 Menthol arm compared to the CC arm, using a one-sided test test with 2.5% type I error probability.

12.5.2 Baseline Comparability

Not applicable.

12.5.3 Descriptive Analysis

Primary endpoints will be summarized as described in Section 12.1.3 on the PP.

12.5.4 Confirmatory Analysis

The hypothesis to be tested is that the geometric mean level of the BoExp for THS 2.2 Menthol is lower relative to mCC.

For primary BoExp, the hypothesis will be tested on Day 5 for monohydroxylbutenyl-mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA), and carboxyhemoglobin (COHb), and on Day 90 Visit for total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) according to the primary and secondary objectives.

Analysis of BoExp will be conducted on the natural log scale. In order to test the follow hypothesis:

Null hypothesis (H0): $m1 \geq m2$

Alternative hypothesis (H1): $m1 < m2$

Where m1 and m2 are the is the geometric means of the biomarker levels on Day 5 or on Day 90 for THS 2.2 Menthol and mCC respectively.

The transformed BoExp data will be analyzed by means of a generalized linear model using product arm as covariate adjusting for the following baseline information: sex, average cigarette consumption over the previous 4 weeks, and baseline value of endpoint. The test will be declared significant if the contrast THS 2.2 Menthol vs mCC is significant. Estimates of differences between groups will be back-transformed to provide relative effects.

Assumptions of the ANOVA model will be tested. Markedly non-lognormally distributed BoExp data will be transformed or analyzed by appropriate non-parametric methods.

Should more than 20% of the subjects be excluded from the PP, would the above confirmatory analysis be repeated on the Compliant Population.

12.6 Secondary Analysis

12.6.1 Secondary Endpoint Analysis Variables

See Section 3.4.2.

More details on derivation rules will be given in the SAP.

12.6.2 Baseline Comparability

Not applicable.

12.6.3 Descriptive Analysis

In general, secondary endpoints will be summarized as described in Section 12.1.3 according to the populations as described in Section 12.4.

12.6.4 Inferential Analysis

For the secondary BoExp and selected risk markers, the hypothesis to be tested is the same as described in Section 12.5.4. This will be tested for secondary BoExp on Day 5, and if significant, on Day 90 (except Total NNAL).

12.6.5 Safety Analysis

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

Adverse events 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; electrocardiogram (ECG) data; clinical chemistry, hematology, concomitant medications, and urine analysis safety panel; physical examination.

The number and percentage of subjects with AEs and SAEs will be tabulated by system organ class (SOC) and preferred term (PT), summarized for the safety population and the full safety population. 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 by sequence for laboratory parameters will be summarized for the safety population and the full safety population. 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 Analysis

12.7.1 Exploratory Endpoint Analysis Variables

See Section 3.4.3.

12.7.2 Descriptive Analysis

In general, exploratory endpoints will be summarized as described in Section 12.1.3 according to the populations as described in Section 12.4.

12.7.3 Preference Analysis

At admission, subjects will be aksed for their preferred product (THS 2.2 Menthol, mCC, no preference). A sensitivity analysis will be run for the exposure according to the subjects' preferred product.

12.8 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be reported according to the populations as described in Section 12.4. Summary statistics will be provided by exposure group and stratified by sex and by cigarette consumption. Formal statistical analysis will not be performed on baseline demographic data.

12.9 Interim Analysis

There are no planned interim analyses.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Principal Investigators and Study Administrative Structure

13.1.1 Principal Investigators

Mamoru Oki M.D., Ph.D.	Seishukai Clinic 3-18-5, Matsugaya, Taitou-ku, Tokyo 111-0036 Japan Phone: [redacted]
Professor Masahiro Endo M.D.	Osaki Hospital Tokyo Heart Center 5-4-12, Kitashinagawa, Shinagawa-ku, Tokyo 141-0001 Japan Phone: [redacted] Fax: [redacted] e-mail: [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
[redacted], PhD Manager Clinical Science	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted], MEng, MSc Staff Scientist (Expert Statistician)	Phone: +41 [redacted] Mobile: +41 [redacted] E-Mail: [redacted]@pmi.com
[redacted], MD Medical Safety Officer	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted], PhD Medical Writer	Phone: +41 [redacted] E-mail: [redacted]
[redacted] Clinical Study Manager	Phone: +41 [redacted] Mobile: +41 [redacted] E-Mail: [redacted]@pmi.com

13.1.3 Other Responsibilities

[redacted] is the local Contract Research Organization designated by PMI to manage and monitor the study: all duties and responsibilities transferred to [redacted] by PMI will be defined in the agreement signed between the two parties.

[redacted]

Responsible person (Clinical Pharmacology): [redacted]

[redacted]

Any SAEs or pregnancies will be handled by:

[redacted]

Phone: [redacted]

Fax: [redacted]

E-mail: [redacted]

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

13.2 Subject Confidentiality

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

The anonymity of subjects participating in this study will be maintained. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on 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 identifiable person (e.g. address, health insurance ID card, medical chart number, etc.). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the subject (e.g. the subject's signed ICF) must be maintained in confidence by the 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, health insurance ID card, 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

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

The Investigator/head of the investigational site and all study site collaborator 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 Principal Investigator/head of investigational 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 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 Article 41 of Ministerial Ordinance on GCP (Ministry of Health and Welfare, 1997). Essential documents

must be retained by the Principal Investigator or the head of the investigational site 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, or
- 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 and Enrolment Log (if applicable).
- Record of all communications between the Principal 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 head of the investigational site has delegated significant study-related duties, together with their roles in the study.
- Investigator Logs.
- eCRFs, study specific questionnaires (and associated data/scoring), subject diaries.
- Adverse event 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, 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 Principal Investigator/head of investigational site as to when these documents no longer need to be retained.

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

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

The head of the investigational site must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If the head of the investigational site 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.

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

13.6 Financial Disclosure

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

13.7 Publication and Disclosure Policy

This document contains 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; however, prompt notice will be given to the Sponsor prior to any such disclosure.

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

13.8 Insurance

The Sponsor is responsible for AEs and health damage of the subjects that are associated with the THS 2.2 Menthol product or with study procedures which are used during this study, except for AEs and health damage of the subjects caused by a negligent or an intentional misconduct and/or significant deviation to the Protocol of the Investigator or the clinical study site or the subjects. The Sponsor has taken out insurance to coverany bodily injury and property damage caused by the operations cried out by the insured. .

14 REFERENCE LIST

Ashley et al., 2008

Ashley DL, Burns D, Djordjevic M, Dybing E, Gray N, Hammond SK, et al. WHO Study Group on Tobacco Product Regulation. The scientific basis of tobacco product regulation. World Health Organ Tech Rep Ser. 2008; (951): 1-277, 1 p following 277.

Aubin et al., 2012

Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ. 2012 Jul 10;345:e4439. doi: 10.1136/bmj.e4439. Available at http:/www.ncbi.nlm.nih.gov/pubmed/22782848

Benowitz et al., 1993

Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. J Am Coll.Cardiol. 1993 Oct; 22 (4): 1159-67.

Benowitz et al., 2002

SNRT subcommittee on biochemical verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002; 4 (2): 149-159.

Cappelleri et al., 2007

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007 May; 32 (5): 912-23.

Chang et al., 1999

Chang GW, Kam PC. The physiological and pharmacological roles of cytochrome P450 isoenzymes. Anaesthesia. 1999 Jan; 54 (1): 42-50.

Connolly et al., 2011

Connolly GN, Behm I, Osaki Y, Wayne GF. The impact of menthol cigarettes on smoking initiation among non-smoking young females in Japan. Int J Environ Res Public Health. 2011; 8 (1): 1-14.

Cox et al., 2001

Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res. 2001; 3 (1): 7-16.

Declaration of Helsinki, 2008

Declaration of Helsinki. 2008. World Medical Association.

Available at:

http://www.wma.net/en/30publications/10policies/b3/index.html (accessed on 21 March 2012).

Eliasson et al., 2001

Eliasson B, Hjalmarson A, Kruse E, Landfeldt B, Westin Å. Effect of smoking reduction and cessation on cardiovascular risk factors. Nicotine and Tobacco Research. 2001; 3: 249-255.

Faber et al., 2004

Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Ther. 2004 Aug; 76 (2): 178-84.

Fagerström et al., 2012

Fagerström K, Russ C, Yu C, Yunis C and Foulds J. The Fagerström Test for Nicotine Dependence as a Predictor of Smoking Abstinence: A Pooled Analysis of Varenicline Clinical Trial. Nicotine & Tobacco Research. 2012; first published online March 30, 2012.

FDA, 2002

Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies, 2002.

Available at:

http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf (accessed 27 Sep 2012).

FDA, 2011

Food and Drug Administration, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments (76 FR 50226, Aug. 12, 2011).

FDA, 2012a

United States Food and Drug Administration, Modified Risk Tobacco Product Applications – Draft Guidance. March 2012.

FDA, 2012b

United States Food and Drug Administration. U.S. Department of Health and Human Services, Cernter for Tobacco Products (CTP), reporting Harmful and Potentially Harmful Cosntituents in Tobacco Products and Tobacco Smoke Under Section 904 (a)(3) of the Federal Food, Drug, and Cosmetic Act, March 2012.

FDA, 2012c

United States Food and Drug Administration. Implementation Specifications, reporting medical device problems, C54451/Medical Device Problem Codes, FDA, CDRH.

Available at:

http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/EventProblemCodes/ucm135741.htm# (accessed on 04 October 2012).

Goniewicz et al., 2009

Goniewicz ML, Havel CM, Peng MW, Jacob P 3rd, Dempsey D, Yu L, Zielinska-Danch W, Koszowski B, Czogala J, Sobczak A, Benowitz NL. Elimination kinetics of the tobacco-specific biomarker and lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Cancer Epidemiol Biomarkers Prev. 2009 Dec;18(12):3421-5.

Frost-Pineda et al., 2008

Frost-Pineda K,. Zedler B, Oliveri D, Liang Q, Feng S, Roethig H. Philip Morris USA. 12-Week clinical exposure evaluation of a third-generation electrically heated cigarette smoking system (EHCSS) in adult smokers. Regulatory Toxicology and Pharmacology 52. 2008; 111–117.

Health Canada, 1999

Health Canada. Determination of “Tar”, Nicotine and Carbon, Monoxide in Mainstream Tobacco Smoke.

Available at: www.hc-sc.gc.ca.

Heatherton et al., 1991

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991; 86 (9): 1119-1127.

Honjo et al., 2010a

Honjo K, Iso H, Tsugane S, Tamakoshi A, Satoh H, Tajima K et al. The effects of smoking and smoking cessation on mortality from cardiovascular disease among Japanese: pooled analysis of three large-scale cohort studies in Japan. Tob Control. 2010; 19 (1): 50-57.

Honjo et al., 2010b

Honjo K, Iso H, Inoue M, Tsugane S; JPHC Study Group. Smoking cessation: predictive factors among middle-aged Japanese. Nicotine Tob Res. 2010; 12 (10): 1050-1054.

Hughes et al., 1986

Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry. 1986 Mar; 43 (3): 289-94.

Hughes et al., 2008

Hughes JR, Hatsukami D. Background on the Minnesota Withdrawal Scale-Revised (MNWS-R). 2008 May; (www.uvm.edu/~hbpl).

Ingelman-Sundberg et al., 1999

Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. Trends Pharmacol Sci. 1999 Aug; 20 (8): 342-9.

Institute of Medicine, 2012

Institute of Medicine Consensus Report. Scientific Standards for Studies on Modified Risk Tobacco Products. Released: December 14, 2011.Board on Population Health and Public Health Practice.

Available at:

http://www.iom.edu/Reports/2011/Scientific-Standards-for-Studies-on-Modified-Risk-Tobacco-Products.aspx

International Tobacco Online, 2012

http://www.internationaltobaccoonline.com/japanese-survey-said-the-percentage-of-smokers-in-japan-is-lower-than-20-p-927.html (accessed 19 June 2012).

Iso et al., 2005

Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, Kikuchi S et al.; JACC Study Group. Smoking cessation and mortality from cardiovascular disease among Japanese men and women: the JACC Study. Am J Epidemiol. 2005; 161 (2): 170-179.

Jacob et al., 2011

Jacob P 3rd, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL. Determination of the Nicotine Metabolites Cotinine and *Trans*-3'-Hydroxycotinine in Biologic fluids of Smokers and Non-smokers using Liquid Chromatography - Tandem Mass Spectrometry: Biomarkers for Tobacco Smoke Exposure and for Phenotyping Cytochrome P450 2A6 Activity. J Chromatogr B Analyt Technol Biomed Life Sci. 2011 Feb 1; 879 (3-4): 267-76.

Lacy et al., 2007

Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15th ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Lindner et al., 2011

Lindner D, Smith S, Martin Leroy C, et al. Comparison of Exposure to Selected Cigarette Smoke Constituents in Adult Smokers and Nonsmokers in a European, Multicenter, Observational Study. Cancer Epidemiol Biomarkers Prev 2011;20:1524-1536. Published OnlineFirst May 25, 2011.

LionCorp.

http://www.lion.co.jp/en/products/html/pro_d036.htm (in English) Contains 500 mg of caffeine anhydrous per 3 tablets.

Ministry of Health and Welfare, 1997

Ministerial Ordinance on Good Clinical Practice for Medical Devices Ordinance of the Ministry of Health and Welfare No. 27, 1997 (As last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 161 of December 28, 2012).

Pilz et al, 2000

Pilz H, Oguogho A, Chehne F, Lupattelli G, Palumbo B, Sinzinger H. Quitting Cigarette Smoking Results in a Fast Improvement of in vivo Oxidation Injury (Determined via Plasma, Serum and Urinary Isoprostane). Thrombosis Research 99 (2000) 209-221.

PMI, 2012a

Philip Morris International. 2013. Internally-modified method based on International Organization for standardization's ISO 4387:2000.. In French. PMI_RD_WKI_000530: Détermination du TMP et CO et trappage de l'eau, nicotine, acide pyruvique et des smoke constituents:BaP, phénols, TSNA et amines aromatiques.

PMI, 2012b

Philip Morris International, 2012. In French. Work Instruction PMI_RD_WKI_000527: Guide d'utilisation de l'extracteur in situ, nettoyage des seringues, des pistons, des aiguilles et des pieges (R2540.M109). Version 3.0.

PMI, 2013a

Philip Morris International, Neuchatel, Switzerland, 2013. Investigator's Brochure for Tobacco Heating System 2.2.

PMI, 2013b

Philip Morris International. 2013. David Ghosh. Experimental report: Identifying the appropriate technique to collect and extract water, nicotine and glycerin from the TPM to further characterize the tar of the ZURICH product. Version 1.0.

PMI White Paper Docket

Food and Drug Administration (FDA), Division of Dockets Management. Philip Morris's International comments on the scientific evaluation of the modified risk tobacco product applications. Docket no. FDA-2011-N-0443.

Raw et al., 2002

Raw M, Anderson P, Batra A, Dubois G, Harrington P, Hirsch A et al. World Health Organization European Partnership Project to Reduce Tobacco Dependence. WHO Europe evidence based recommendations on the treatment of tobacco dependence. Tob Control. 2002; 11 (1): 44-46.

Saareks et al., 2001

Saareks V, Ylitalo P, Alanko J, Mucha I, Riutta A. Effects of smoking cessation and nicotine substitution on systemic eicosanoid production in man. Naunyn Schmiedebergs Arch Pharmacol. 2001 May; 363 (5): 556-61.

Tiffany et al., 1991

Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. British Journal of Addiction. 1991; 86: 1467-1476.

U.S. Department of Health and Human Services, 2010

U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

Available at:

http://www.surgeongeneral.gov/library/tobaccosmoke/report/executivesummary.pdf

Vasan, 2006

Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006 May 16; 113 (19): 2335-62.

YVD-CS01-EU study

Philip Morris International, 2009. YVD-CS01-EU study. A Controlled, Randomised, Open-Label, 3-Arm Parallel Single-Centre Confinement Study to Investigate Exposure to Selected Smoke Constituents in Smokers Switching From Conventional Cigarettes to SMAR Cigarettes for 5 Days (ClinicalTrials.gov: ID: NCT00812279).

Available at:

http://clinicaltrials.gov/show/NCT00812279 (accessed on 22 February 2013)

Appendix 1 Schedule of Events

Table A1 Study Assessments (separate table [Table A2] shown for 24 hour urine collections)

	Screening	Confinement Period								Ambulatory Period							Safety Follow-up [v]
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30**	**31**	**60**	**61**	**90**	**91**	**91 to 119**
Informed consent for study participation and two informed consents for bio-bankings	●																
Admission/Discharge		●								●						●	
Advice on the risk of smoking and debriefing	●	●								●		●		●		●	
Monitoring/Intensive support for SA arm					●	●	●	●	●	●	●	●	●	●	●		
Inclusion/exclusion criteria	●	●															
Enrolment		●															
Randomization				●													
Demographics, medical history,	●																
Concomitant diseases	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	

	Screening	Confinement Period								Ambulatory Period							Safety Follow-up [v]
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30**	**31**	**60**	**61**	**90**	**91**	**91 to 119**
Socio-economic questionnaire								●									
Vital signs [a]	●	●	●	●	●	●	●	●	●	●	●		●			●	
Physical examination	●	●								●	●		●			●	
Body height and weight [b]	●	●								●	●		●			●	
Waist circumference [c]		●														●	
Spirometry [d]	●			●						●						●	
Prior/concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
B/U: Hematology, clinical chemistry, urine analysis [e]	●			●						●		●		●		●	
Electrocardiogram	●									●	●		●			●	
Chest X-ray [f]	●																
B: HIV, hepatitis B and C	●																
U: Urine drug screen, urine cotinine screening test	●	●															
U: Pregnancy test	●	●								●		●		●		●	
Alcohol breath test	●	●															
FTND	●														●		

	Screening	Confinement Period								Ambulatory Period							Safety Follow-up [v]
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30**	**31**	**60**	**61**	**90**	**91**	**91 to 119**
Smoking history	●	●															
Willingness to quit smoking in the next three months	●																
Readiness to abstain from smoking up to 90 days	●	●															
Identification of mCC	●	●															
THS 2.2 Menthol demonstration	●																
THS 2.2 Menthol product test [g]		●															
Collection of mCC butts for accountability			●	●	●	●	●	●	●	●							
Collection tobacco plugs of used Menthol Tobacco Sticks for further analysis					●	●	●	●	●		●		●		●		
Collection filters of used Menthol Tobacco Sticks for further analysis					●	●	●	●	●								

	Screening	Confinement Period								Ambulatory Period						Safety Follow-up [v]
										Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30**	**31**	**60**	**61**	**90**	**91**	**91 to 119**
Collection filters of used Menthol Tobacco Sticks for accountability					●	●	●	●	●	●							
Collection of empty/partially used Menthol Tobacco Stick packs											●		●		●		
CO breath test [h]		●	●	●	●	●	●	●	●	●	●		●		●		
B: BoExp in blood: COHb [i]			●	●	●	●	●	●	●		●		●		●		
B: BoExp to nicotine in plasma: nicotine, cotinine [j]				●	●	●	●	●	●	●	●		●		●		
U: Ames Mutagenicity (see Table A2)				●					●						●		
U:all urinary BoExp (primary and secondary, and BoExp to nicotine) [j] (see Table A2)			●	●	●	●	●	●	●		●		●		●		
B:Risk markers: hs-CRP, fibrinogen, homocysteine, LDL, HDL [k]				●								●		●		●	

	Screening	Confinement Period								Ambulatory Period							Safety Follow-up [v]
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30**	**31**	**60**	**61**	**90**	**91**	**91 to 119**
B: Risk Marker: s-ICAM-1 [l]				●						●		●		●		●	
B: Risk Marker: HbA1c [m]				●												●	
U: Risk markers: 8-epi-PGF2α and 11-DTX-B2 (see Table A2) [n]				●					●		●		●		●		
One caffeine tablet (170mg)				●					●						●		
B: CYP1A2 activity				●					●						●		
B: CYP2A6 activity				●						●						●	
Product use diary [o]										●	●	●	●	●	●		
QSU-brief questionnaire [p]			●	●	●	●	●	●	●		●		●		●		
MNWS (revised version) [q]				●	●	●	●	●	●	●		●		●		●	
MCEQ (modified version; THS 2.2 Menthol and mCC arms) [r]			●	●	●	●	●	●	●		●		●		●		
HST (THS 2.2 Menthol and mCC arms) [s]				●	●			●			●		●		●		
HST questionnaire				●				●			●		●		●		
Assessment of cough [t]				●	●	●	●	●	●	●		●		●		●	

	Screening	Confinement Period								Ambulatory Period						Safety Follow-up [v]
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days	
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30**	**31**	**60**	**61**	**90**	**91**	**91 to 119**
Preference product question		●															
AE/SAE recording	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
U: Bio-banking for BoExp and risk markers (see Table A2) [u]				●					●						●		
B: Bio-banking for BoExp and risk markers [u]				●						●						●	
B: Bio-banking for transcriptomics [u]				●						●						●	

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; B = blood sample required; BMI = body mass index; BoExp = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; FTND = Fagerström Test for Nicotine Dependence; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; HST = human smoking topography; HIV = human immunodeficiency virus; hs-CRP = high-sensitive C-reactive protein; LDL = low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; THS = tobacco heating system; U = urine sample required; WBC = white blood cell count; TC: total cholesterol, TG: triglycerides.

a: Systolic and diastolic blood pressure, pulse rate, and respiratory rate (systolic and diastolic blood pressure will also be evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 91)).

b: Including height (only at Screening), body weight and calculated BMI. Weight will be evaluated also as risk marker on Day 0 and Day 90 Visit (Day91)

c: Waist circumference will be evaluated also as risk markers on Day -2 and Day 90 Visit (Day 91).

d: At screening, spirometry without bronchodilator will be done first, and then, spirometry with bronchodilator. At screening, spirormetry has to be conducted at least 1 hour after smoking. Furthermore, spirometry without bronchodilator will be performed prior to product use at Day 0 (baseline values), on Day 6, and Day 90 Visit (on Day 91 for comparison with the baseline values).

e: WBC, platelet count, from the safety laboratory panel to be evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61) and Day 90 Visit. (Day 91) Blood glucose, TG, and TC from the safety laboratory panel to be evaluated also ed as risk markers on Day 0, Day 30 Visit (Day 31) , Day 60 Visit (Day 61), and Day 90 Visit (Day 91).

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

g: THS 2.2 Menthol product test to be conducted as the last procedure of eligibility check at Day -2 (and after urine pregnancy test has been confirmed negative in female subjects to exclude pregnancy).

h: CO breath test; Days -1 to Day 5: the test will be conducted four times per day. The first test should be conducted within 15 minutes prior to the first product use (for subjects in the Menthol 2.2 and mCC arms) and between 08:00 AM-09:30 AMfor subjects in the SA arm. The other three tests should be conducted as described in section 9. Day -2, Day 6, Day 30 Visit (Day 30) , Day 60 Visit(Day 60) and Day 90 Visit (Day 90): once during the visit, irrespective of the time of product use.

i: COHb; Assessments should be done in conjunction with CO breath tests, where applicable. Day -1 to Day 4: one blood sample in the evening between08:00 PM-09:30 PM.

Day 5: one blood sample within 15 minutes prior to product use (for subjects in THS 2.2 Menthol and mCC arms) and between 08:00 AM_09:30 AM for subjects in the SA arm. The three other blood sampling will be conducted as described in section 9.

Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90): one blood sample to be collected during the visit, irrespective of the time of product use.

j: Nicotine/cotinine; Day 0 to Day 4 (all study arms): one blood sample between 08:00 PM-09:30 PM.

Day 5 and Day 6 (THS 2.2 Menthol and mCC arms): one sample within 15 minutes prior to the product use; eight blood samples after product use (T0), each at 2 hour intervals. On Day 6, two blood samples will be drawn. The first sample will be 20 hours after T0 and the second blood sample will be 24 hours after T0 (with T0 being the time of the first product use on Day 5).

Day 5 and Day 6 (SA arm): on Day 5, one blood sample in the evening betwen 08:00 PM-09:30 on Day 5 and one blood sampling between 08:00 AM-09:30 AM on Day 6.

Day 30 Visit (Day 30) , Day 60 Visit (Day 60) , Day 90 Visit (Day 90) (all study arms): one blood sample to be drawn during the visit, irrespective of the time of product use.

k:To be evaluated also as risk markers on Day 0, Day 30 Visit (Day 31), Day 60 Visit (Day 61) , and Da y 90 Visit (Day 91).

l: . To be evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 31) , Day 60 Visit (Day 61) , and Da y 90 Visit (Day 91).

m: To be evaluated also as risk markers on Day 0, and Da y 90 Visit (Day 91).

n: To be evaluated also as risk markers on Day 0, Day 5, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day90).

o: Daily during ambulatory period only (from time of Discharge on Day 6 to Day 90 only). Use of any tobacco/nicotine containing products will be captured in the e-diary.

p: QSU-brief: Daily, from Day -1 to Day 5 and at every visit during the ambulatory period, i.e. Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90).

q: MNWS daily from Day 0 to Day 6 prior product use but no later than 10: 00 AM and at every visit during the ambulatory period no later than 10:00 AM, i.e. Day 30 Visit (Day 31), and Day 60 Visit (Day 61) irrespective of time of product use and on Day 90 Visit (Day 91) prior to smoking.

r: MCEQ: Day -1 to Day 5 on a daily basis, and on Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90). On Day -1 and Day 0, MCEQ will be aksed to all subjects. From Day 1, MCEQ will be asked to THS 2.2 Menthol and mCC arms only.

s: On Day 0, HST assessment will be done in all subjects smoking mCC compatible with the HST SODIM® device. On Day 1, Day 4, Day 30 Visit, (Day 30) and Day 60 Visit (Day 60) and Day 90 Visit (Day 90), HST. Smoking topography with the HST device will not be done in subjects smoking mCC that are incompatible with the HST SODIM® device (e.g. slim mCC). No HST assessments will be done in subjects in the SA arm.

t: cough questionnaire to be done daily from Day 0 to Day 6 prior product use but no later than 10: 00 AM and at every visit during the ambulatory period no later than 10:00 AM, i.e. Day 30 Visit (Day 31), and Day 60 Visit (Day 61) irrespective of time of product use and Day 90 Visit (Day 91) prior to smoking.

u: Samples will only be taken if additional consent for bio-banking is given by the subject.

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

Table A2 Schedule for 24 hour Urine Collection Assessments

During the confinement and ambulatory periods, the dot corresponds to the start of 24-hour urine collection.

	Baseline period		Confinement Exposure Period 24-hour urine					Ambulatory Exposure Period 24-hour-urine		
	Day -1 to Day 0	Day 0 to Day 1	Day 1 to Day 2	Day 2 to Day 3	Day 3 to Day 4	Day 4 to Day 5	Day 5 to Day 6	Day 30 to Day 31	Day 60 to Day 61	Day 90 to Day 91
BoExp in urine [a]	●	●	●	●	●	●	●	●	●	●
Creatinine	●	●	●	●	●	●	●	●	●	●
11-DTX-B2 and 8-epi-PGF2α		●					●	●	●	●
Ames mutagenicity test		●					●			●
Bio-banking [b]		●					●			●

Abbreviations: Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2

[a] MHBMA, 3-HPMA, S-PMA, total NNAL, 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, 3-hydroxybenzo(a)pyrene, HMPMA, S-BMA, NEQ.

b: Samples will only be taken if additional consent for BoExp bio-banking is given by the subject.

During the confinement and ambulatory periods, when the BoExp is mentioned to be assessed at Day x, it corresponds to the start of urine collection, For example, for NEQ assessed on Day 5, it will be the measurement of NEQ in the Day 5-Day 6 24-hour urine collection.

Appendix 2 Participating Laboratories

[redacted]

More details will be found in the study laboratory manuals.

For samples biobanking:

[redacted]

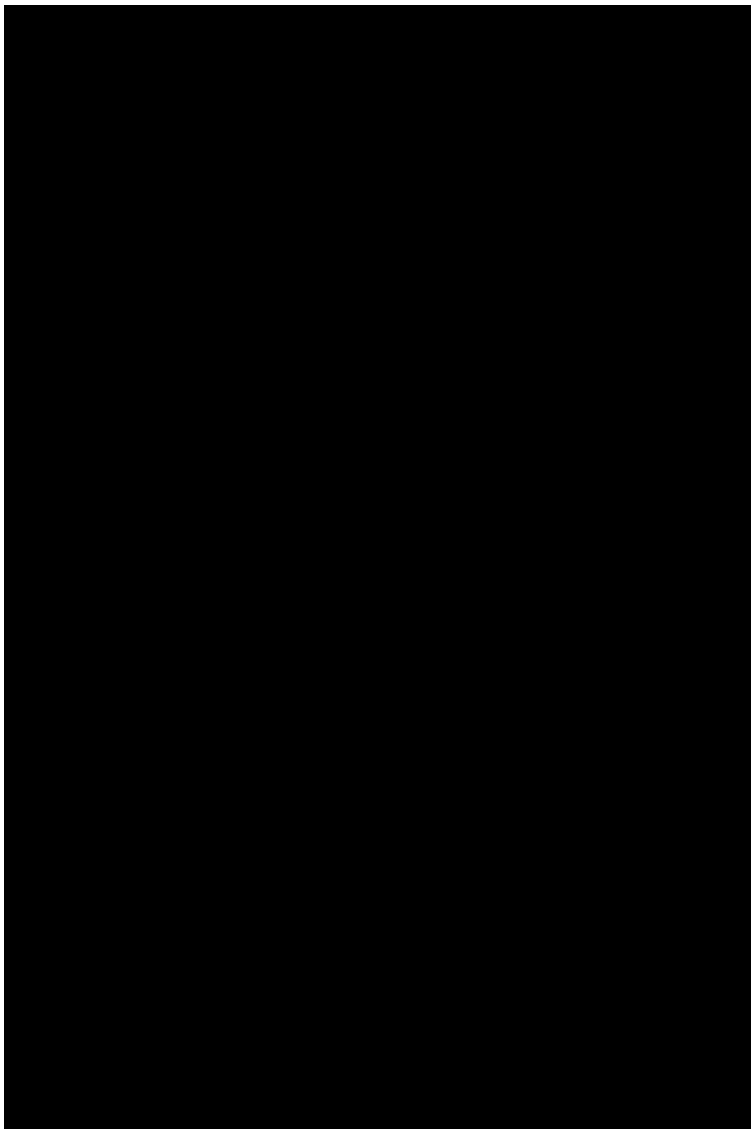
[redacted]

Appendix 3 Investigational Product and Instructions for Use

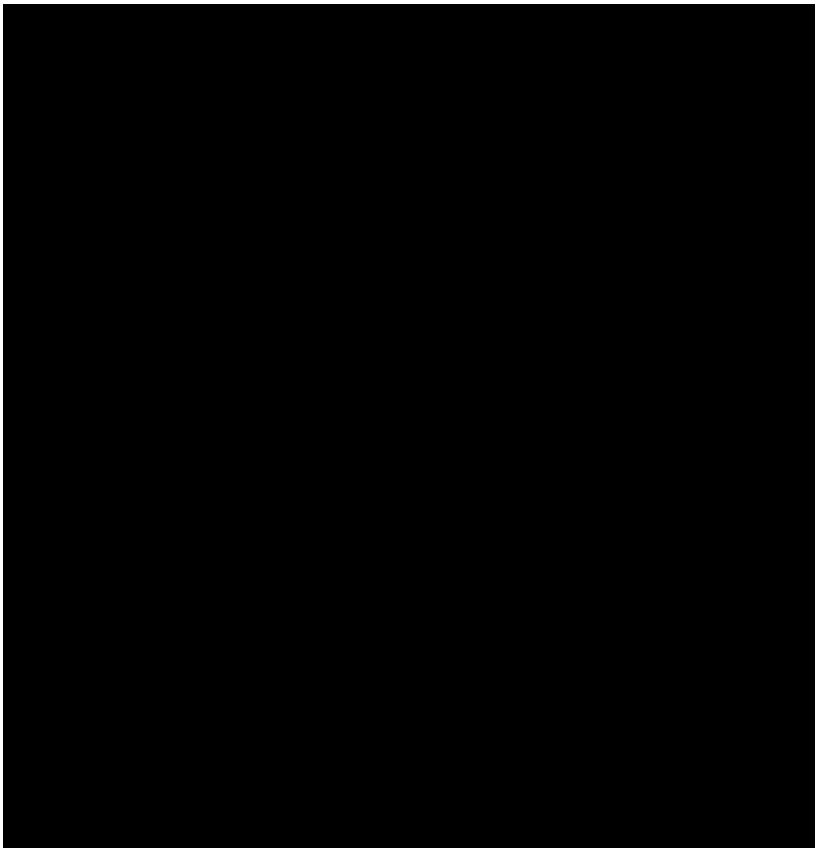
The product user guide will be provided as a separate document.

Appendix 4 THS Package Labels

The package label for the THS Menthol Tobacco Sticks:

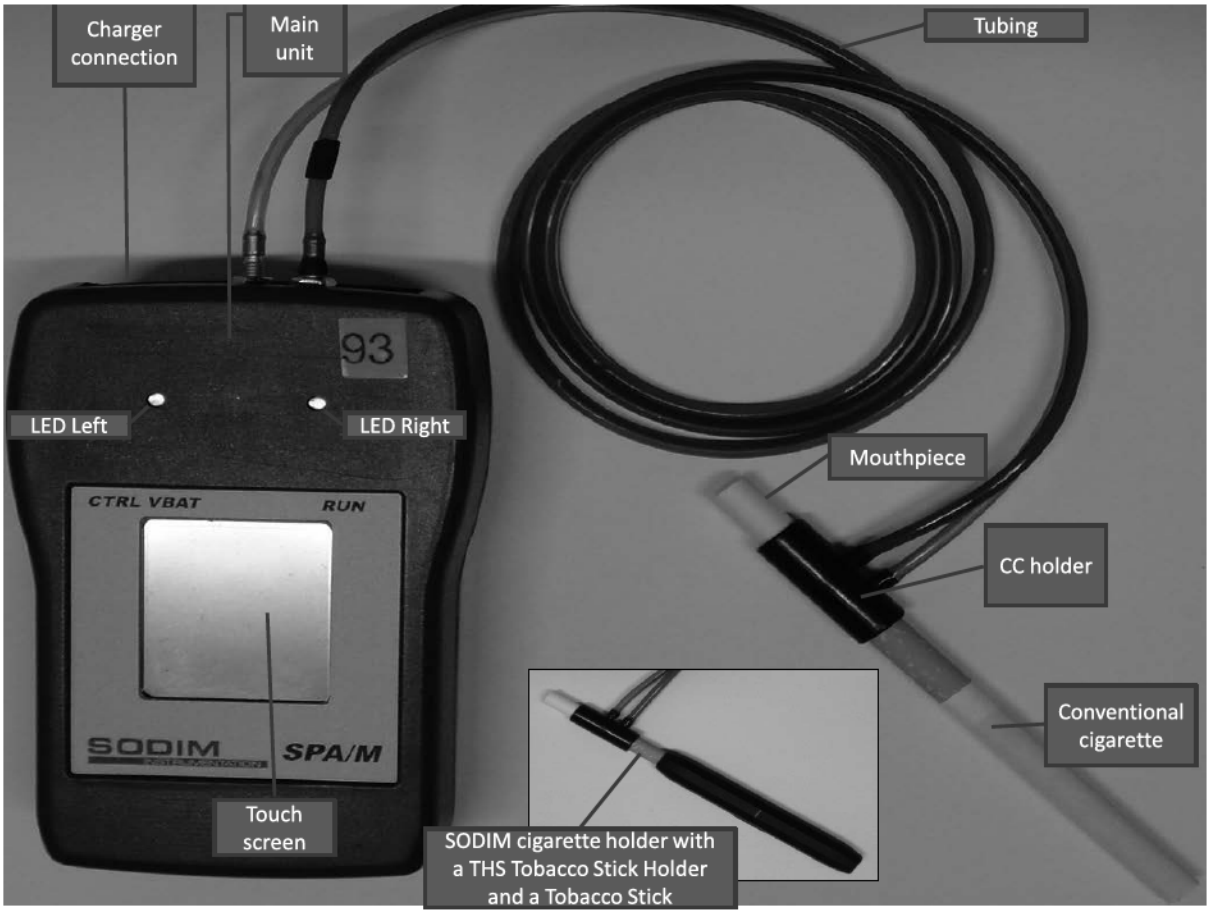


The package label for the THS Menthol Tobacco Sticks carton:



Appendix 5 SODIM® Device Description

An image of the SODIM® device used for assessing Human Smoking Topography (HST) is provided below. Full instructions for use of the device will be provided to the study collaborators before study start.



Appendix 6 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
Glucose – Hyperglycemia: ** (1)			
Fasting (mg/dl)	>ULN – 160;	>160 – 250;	-
(mmol/l)	>ULN – 8.9	>8.9 – 13.9	-
Non-fasting (mg/dl)	-	-	>250 – 500;
(mmol/l)	-	-	>13.9 – 27.8; hospitalization indicated
Blood Urea Nitrogen (BUN) (mg/dl) (2)	23 – 26	27 – 31	> 31
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 ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 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; LLN = lower limit of the normal range; ULN = upper limit of the normal range.

Data Sources:

(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) change from baseline value – (g/dl) (1)	11.0 – 12.0 Any decrease – 1.5	9.5 – 10.9 1.6 – 2.0	8.0 – 9.4 2.1 – 5.0
Hemoglobin (Male) – (g/dl) (1) change from baseline value – (g/dl) (1)	12.5 – 13.5 Any decrease – 1.5	10.5 – 12.4 1.6 – 2.0	8.5 – 10.4 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; IV = intravenous.

Data Source:

(1) Common Terminology Criteria for Adverse Events (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.