PMI RESEARCH & DEVELOPMENT

# Clinical Study Protocol
# ZRHR-REXC-03-EU

| | |
|---|---|
| **Study title:** | A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement |
| **Short study title:** | Reduced exposure study in smokers using THS 2.2 with 5 days in a confinement setting |
| **Registration number:** | Not assigned |
| **Product name:** | Tobacco Heating System 2.2 (THS 2.2) |
| **Sponsor:** | Philip Morris Products S.A.<br>Quai Jeanrenaud 5<br>2000 Neuchâtel<br>Switzerland |
| **Version number:** | Final |
| **Revision date:** | 25 April 2013 |
| **Authors:** | [redacted] PhD, Manager Clinical Science<br>[redacted], MEng MSc, Biostatistician<br>[redacted], MD, Medical Safety Officer<br>[redacted], Medical Writer |

# SYNOPSIS

**Sponsor:**

Philip Morris Products S.A.

**Name of Product:**

Tobacco Heating System 2.2 (THS 2.2)

**Study Title:**

A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement

**Short Study Title:**

Reduced exposure study in smokers using THS 2.2 with 5 days in a confinement setting

**Study Number:**

ZRHR-REXC-03-EU

**Primary Objective**

The primary objective of this study is:

- To demonstrate the reduction of primary biomarkers of exposure (BoExp) in smokers switching from conventional cigarettes (CC) to THS 2.2 as compared to smokers continuing to smoke CC.

**Secondary Objectives**

The secondary objectives of this study are:

- To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To determine the levels of nicotine on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.
- To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to smoking abstinence (SA).
- To describe the pharmacokinetic profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

- To describe the changes in Cytochrome P450 1A2 enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.
- To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To monitor the safety profile during the study.

**Exploratory Objectives**

The exploratory objectives of this study are:

- To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and smokers switching from CC to SA:
    - Excretion of mutagenic material in urine.
    - Subjective effects of smoking.
    - CYP2A6 activity, and
    - Selected risk markers.

- To evaluate in smokers switching from CC to THS 2.2, smokers continuing to smoke CC and smokers switching from CC to SA the relationship between:
    - Nicotine equivalents (NEQ) and primary and secondary BoExp.
    - Selected risk markers and primary, secondary BoExp, and NEQ.

- To describe the following parameters over the course of the study in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:
    - Product evaluation.
    - Smoking pattern.

- To describe the following parameter over the course of the study in smokers switching from CC to THS 2.2:
    - Potential combustion occurrences in tobacco plugs.
    - Filter analysis.

Study Hypotheses:

The hypothesis to be tested for each of the primary and secondary BoExp is that the geometric mean level on Day 5 of the biomarker for THS 2.2 is lower relative to CC.

**Study Endpoints**:

The primary and secondary BoExp measured in this study are presented in Table S1.

Table S1:

| | **Biomarkers of Exposure (BoExp)** | **Harmful and potentially harmful constituents (HPHCs)** | **Matrix** |
|---|---|---|---|
| Primary BoExp | monohydroxybutenyl mercapturic 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 |
| Secondary BoExp | carbon monoxide | CO | Exhaled breath |
| | total 1-hydroxypyrene (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-hydroxyethyl mercapturic acid (HEMA) | ethylene oxide | Urine |
| | 3-hydroxy(a)benzopyrene | benzo(a)pyrene | Urine |
| | 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) | crotonaldehyde | Urine |
| | S-benzylmercapturic acid (S-BMA) | toluene | Urine |
| | total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) | 4 -(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) | Urine |

| | | | |
|---|---|---|---|
| BoExp to nicoitne | nicotine equivalents (NEQ)<br>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:

- To demonstrate the reduction of primary BoExp in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.
    - Monohydroxybutenyl mercapturic acid, 3-hydroxypropylmercapturic acid, S-phenylmercapturic acid (concentration adjusted to creatinine) in 24-hour urine, and carboxyhemoglobin in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

Evaluation Criterion: The study will be considered successful if the study demonstrates a 50% reduction or more for all four primary BoExp in the THS 2.2 arm compared to the CC arm (as measured on Day 5).

Secondary endpoints:

- To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
    - BoExp listed as secondary (Table S1) for the comparison of levels between smokers switching from CC to THS 2.2 and smokers continuing to smoke CC as measured on Day 5 as follows:
        - Carbon monoxide (CO) (expressed as ppm) in exhaled breath.
        - Urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

- To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
    - BoExp listed as primary and secondary (Table S1) for the comparison of levels between smokers switching from CC to THS 2.2 and smokers continuing to smoke CC as measured from Day 1 to Day 5.

- 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 on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.
  - NEQ (expressed in quantity excreted and concentration adjusted to creatinine) (Table S1) in 24-hour urine on Day 5 and from Day 1 to Day 5.
  - Nicotine and cotinine in plasma on Day 5 and from Day 1 to Day 5.

- To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to SA.
  - BoExp listed as primary and secondary (Table S1) from Day 1 to Day 5 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 describe the PK profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
  - Peak (highest concentration value along the day) on Day 5 in plasma.
  - 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 changes in CYP1A2 enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.
  - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5.

- To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:
    - Number of THS Tobacco Sticks and CC used each day for each subject from Day 1 to Day 5.

- To monitor the safety profile during the study:
    - AEs/ SAEs and device events including THS 2.2 malfunction/misuse.
    - Respiratory symptoms: cough assessment by visual analogue scale (VAS), Likert scales, and one open question.
    - Vital signs.
    - Spirometry.
    - Electrocardiogram (ECG).
    - Clinical chemistry, hematology, and urine analysis safety panel.
    - Physical examination.
    - Concomitant medications.

Exploratory Endpoints

- To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to smokers switching from CC to SA:
    - Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 in 24-hour urine.
    - Subjective effects of smoking: Questionnaire of Smoking Urges (brief version) (QSU-brief); Minnesota Nicotine Withdrawal Scale, revised version on Day 5.
    - CYP2A6 enzymatic activity: in plasma on Day 6, using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.
    - Selected risk markers: 8-epi-prostaglandine F2α (8 epi-PGF2α) and 11 dehydro thromboxane B2 (11-DTX-B2) measured in 24-hour urine on Day 5.

- To evaluate in smokers switching from CC to THS 2.2, smokers continuing to smoke CC, and smokers switching from CC to SA the relationship between:
    - NEQ and primary and secondary BoExp in 24-hour urine on Day 5.

- Primary, secondary BoExp, NEQ, and risk markers (8 epi-PGF2α and 11-DTX-B2) in 24-hour urine.

- To describe the following parameters over the course of the study in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:
  - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
  - 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 CC to THS 2.2:
  - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
  - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm.

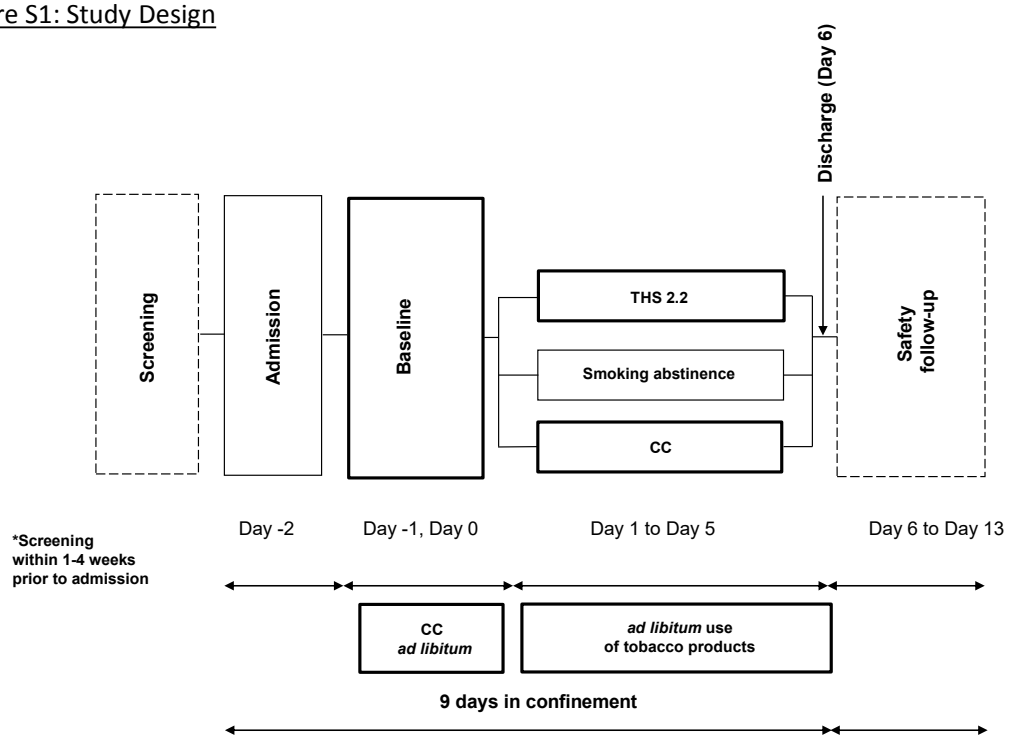
**Study Design:**

A randomized, controlled, open-label, 3-arm, parallel group, single-center study 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 to 19 CC and smokers smoking >19 CC per day) (Figure S1).

This is an *ad libitum* smoking study. In general, smoking during confinement will be allowed between 06:30 AM and 11:00 PM.

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 and CC in THS 2.2 and CC arms respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each Tobacco Stick/CC on demand of the subject.

Figure S1: Study Design




Abbreviations: THS 2.2 = Tobacco Heating System 2.2; CC = conventional cigarettes.

- Screening period over 4 weeks (Day -30 to Day -3) prior to admission to the clinic (Day -2):

  A demonstration of the THS 2.2 product will be done by the site staff during the Screening Visit. Subjects will be in a confinement setting for 9 days from Day -2 onwards. Screening procedures do not necessarily have to be conducted on the same day.

- 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 (use of up to 3 THS 2.2 Tobacco Sticks). In female subjects, the THS 2.2 product test may 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.

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

  All subjects will continue smoking their single preferred brand of CC and

baseline values will be recorded. On Day 0, subjects will be randomized to one of the 3 study arms in a 2:1:1 ratio using a stratified randomization:

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

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

- Exposure period (from Day 1, 06:30 AM until Day 5, 11:00 PM):

  The exposure period will consist of 5 days of *ad libitum* use of the assigned product between 06:30 AM and 11:00 PM in the THS 2.2 and CC arms. Use of any tobacco/nicotine-containing product other than the assigned product will not be allowed and may, at the discretion of the Investigator or designee, result in the subject withdrawal from the study.

  Subjects in the SA arm will be asked to abstain from smoking any nicotine/tobacco-containing product and will not be provided with medication to support SA. Subjects will be provided with psychological support during the period of smoking abstinence.

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

- Day of Discharge (Day 6) (from Day 5, 11:01 PM to time of Discharge):

  Procedures of Discharge, including but not limited to laboratory parameters, will be conducted to discharge the subject from the clinic after 9 days in a confined setting. Use of CC will be allowed on Day 6, but only after spirometry has been performed.

- Safety follow-up period (from Day 6, time of Discharge to Day 13):

  After time of Discharge, subject will enter a 7-day safety follow-up during which there will be recording of spontaneously reported new adverse events (AEs)/serious adverse events (SAEs) and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be actively followed 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 6 plus 7-day follow-up period.

  During the study, any subjects who want to quit smoking will receive appropriate medical advice and will be referred to a smoking cessation councilor.

**Study Population and Main Criteria for Inclusion:**

One hundred and sixty female or male smoking, healthy Caucasian adult subjects meeting the following main inclusion criteria:

- Subject is aged from 21 to 65 years (inclusive).
- Subject is Caucasian.
- Smoking, healthy subject as judged by the Investigator or designee.
- Subject smokes at least 10 commercially available non-menthol CCs 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.
- The subject is ready to accept 5 days of smoking abstinence.
- The subject is ready to accept using the THS 2.2 product.

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

**Investigational Product; Dose; and Mode of Use:**

Test Product: Tobacco Heating System 2.2 (THS 2.2)

Reference product: The reference product to the THS 2.2 during the randomized exposure period is the subject's own preferred commercially available single brand of non-menthol CC

Reference Point: SA

**Duration of Study:**

The entire study duration per subject will be 17 to 44 days, including a Screening period of up to 4 weeks prior to baseline (Day -30 to Day -3), a 9-day confinement period (from Day -2 to time of Discharge on Day 6), followed by a 7-day safety follow-up period (until Day 13).

**Statistical Methods:**

Statistical Analysis:

Analysis of BoExp will be conducted on the natural log scale. The transformed 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. Estimates of differences between groups will be back-transformed to provide relative effects. Assumptions of the analysis of variance model will be tested. Markedly non-lognormally distributed BoExp data will be transformed or analyzed by appropriate non-parametric methods.

Unless stated otherwise, all statistical tests will be two-sided and conducted at the 5%

level, and all quoted confidence intervals (CIs) will be two-sided 95%CIs.

Sample Size:

A total of 160 subjects (80 in the THS 2.2 arm, 40 in the CC arm, and 40 in the SA arm) will be randomized. This sample size is needed to attain 80% power to show demonstrate a reduction of at least 50% on four primary BoExps in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC, using one-sided test with 2.5% type I error probability.

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## Abbreviations

| | |
|---|---|
| 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 |
| 11-DTX-B2 | 11-dehydro-thromboxane B2 |
| ADL | Activities of daily living |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| BoExp | Biomarker(s) of exposure |
| BUN | Blood urea nitrogen |
| CAF | Caffeine |
| CC | Conventional cigarette(s) |
| CD | Compact Disc |
| CEMA | 2-cyanoethylmercapturic acid |
| CI | Confidence interval |
| CO | Carbon monoxide |
| COHb | Carboxyhemoglobin |
| 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 |
| EOS | End of Study |
| ePRO | Electronic patient 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 |
| Hb | Hemoglobin |
| HbsAg | Hepatitis B surface antigen |
| Hct | Hematocrit |
| HCV | Hepatitis C virus |
| HEMA | 2-hydroxyethyl mercapturic acid |
| HIV | Human immunodeficiency virus |
| HMPMA | 3-hydroxy-1-methylpropylmercapturic acid |
| HPHCs | Harmful and potentially harmful constituents |
| HST | Human smoking topography |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |

| | |
|---|---|
| IEC | Independent Ethics Committee |
| IP | Investigational Product |
| ISO | International Organization for Standardization |
| IV | Intravenous |
| IWRS | Interactive Web and Voice Response System |
| LDH | Lactic dehydrogenase |
| LLN | Lower limit of the normal range |
| LLOQ | Lower limit of quantification |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCEQ | Modified Cigarette Evaluation Questionnaire |
| 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 |
| n | number of subjects |
| 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 |

| | |
|---|---|
| PX | Paraxanthine |
| QC | Quality control |
| QSU-brief | Questionnaire of Smoking Urges (brief version) |
| RBC | Red blood cell |
| RNA | Ribonucleic acid |
| SA | Smoking abstinence |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| S-BMA | *S*-benzylmercapturic acid |
| SHM | Sample Handling Manual |
| SOP | Standard Operating Procedure |
| S-PMA | *S*-phenylmercapturic acid |
| THS 2.2 | Tobacco Heating System 2.2 |
| U | Urine |
| [redacted] | [redacted] |
| UK | United Kingdom |
| ULN | Upper limit of the normal range |
| ULOQ | Upper limit of quantification |
| VAS | Visual analogue scale |
| WBC | White blood cell |
| WHO | World Health Organization |

## Explanation of Terms

The following special terms are used in this protocol:

| | |
|---|---|
| Baseline period | 06:30 AM at Day -1 until 06:29 AM of Day 1. |
| 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. |

| | |
|---|---|
| CC | The term 'conventional cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products. |
| CC incompatible with HST device | All CCs that are incompatible with the HST device (e.g. slim CC). |
| Day of Discharge | Day 6 |
| End of the study | End of Study is defined as the time of discharge on Day 6 plus 7-day follow-up period. |
| 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 THS 2.2 (the test of THS 2.2 is the last assessment prior to enrolment). |
| Exposure period | 06:30 AM of Day 1 until 11:00 PM of Day 5. |
| 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, a 7-day safety follow-up will be done for the recording of spontaneously reported new adverse events (AEs)/serious adverse events (SAEs) and the active follow-up of ongoing AEs/SAEs. In general, any AE will be actively followed-up until resolved, stabilized, (i.e., no worsening of the event), or a plausible explanation for the event has been found. |
| Screening failure | Subjects who do not meet the entry criteria from informed consent form (ICF/subject information sheet) signature to the time of enrolment will be considered a screening failure and will be replaced by other subjects. |

| | |
|---|---|
| Time of Discharge | The time of day the subject is discharged on Day of Discharge. |
| 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). |
| Tobacco Heating Device | The Device comprises everything in THS 2.2 except the Tobacco Stick |
| Tobacco Heating System 2.2 (THS 2.2) | THS 2.2 comprises the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable. |
| THS Tobacco Stick (Tobacco Stick) | The THS Tobacco Stick (Tobacco Stick) (product code C3) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder. |

# 1 ETHICS AND REGULATIONS

## 1.1 Independent Ethics Committee Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF], subject information sheet, subject recruitment procedures [e.g., advertisements], written information including questionnaires and instructions to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC. The IEC shall be appropriately constituted and perform its functions in accordance with the International Conference on Harmonization (ICH) Tripartite Guidance for Good Clinical Practice (GCP) and local requirements, as applicable.

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

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

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

These requirements for approval should in no way prevent any action from being taken by the Investigator (or designee) 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 or designee, and is implemented for safety reasons, the Sponsor and the IEC should be informed immediately.

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

## 1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, 2008 and are consistent with ICH/GCP applicable regulatory principles.

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

## 1.3 Subject Information and Consent

### 1.3.1 Informed Consent Form/Subject Information Sheet for Participation to the Study

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

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

The subject will be informed that additional data analyses not mentioned in the protocol or the statistical analysis plan might be performed with the collected data at a later time. If any additional analyses will be performed, they will fully be covered by data confidentiality, as for the main analyses described in this protocol.

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

#### 1.3.2.1 Bio-banking 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 pharmacogenomics testing will be done on these samples.

#### 1.3.2.2 Bio-banking for Transcriptomics (Pharmacogenomics)

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 as

compared to smokers continuing to smoke CC 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 or designee 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 person who conducted the informed consent discussion. The subject's consent to storage of any samples in a bio-bank 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/ subject information sheet. If revision of the ICF/subject information sheet is necessary, the Investigator or designee will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IEC before subjects are required to re-sign the ICF/subject information sheet.

## 1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator or designee 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 applicable national and local laws of the pertinent regulatory authorities.

# 2 INTRODUCTION

## 2.1 Background

### 2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette smoking causes pulmonary and cardiovascular diseases and other serious diseases in smokers (U.S. Department of Health and Human Services, 2010). There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers cannot refrain from smoking or decide to continue smoking. To those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases. These products are now referred to by the United States Food and Drug Administration (FDA) as modified risk tobacco products (MRTPs) (Food and Drug Administration, 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 conventional cigarettes [CC]). Philip Morris International is developing candidate MRTPs that provide an inhalation experience without combustion. The novel approach to achieve this is by heating tobacco at significantly lower temperatures than required for CC.

Philip Morris International'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 (SA) as the reference point for assessing the risk reduction potential of its candidate MRTPs. The Institute of Medicine refers to smoking cessation as 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). Philip Morris International has 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 reduction of individual risk in smokers and reduction of population harm.

### 2.1.2 Description of the Product and Scientific Findings

Thousands of chemicals - "smoke constituents" - are formed when tobacco is burned or combusted. More than 5,300 smoke constituents have been identified (Rodgman and Perfetti, 2009), and more than 100 of them have been categorized as harmful and potentially harmful

constituents (HPHCs) (Food and Drug Administration, 2011). There is no convincing evidence that selective reduction of smoke constituents can reduce tobacco related diseases (Hatsukami et al, 2007). Philip Morris International's focus has been the development of products that do not combust tobacco but which replicate the "smoking experience" traditionally obtained with CC, as much as possible. Our approach limits pyrolysis and combustion, by heating tobacco at significantly lower temperatures than CC. Philip Morris International believes that such products present the best opportunity for reducing harm because they produce vastly lower levels of HPHCs and are more likely to be accepted by smokers as substitutes for CCs. Important to this effort has been providing nicotine in a way that closely parallels CC.

The product developed by PMI, and to be assessed in this study, is the Tobacco Heating System 2.2 (THS 2.2). 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 is composed of the 'THS Tobacco Stick Holder', dedicated special 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 minute session. Unlike CC, the Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of THS 2.2 and its predecessors including THS 1.0 supports the initiation of the clinical studies described in this Investigator's Brochure (PMI, 2013a). No new or increased toxicological hazard in the product's aerosol was detected, compared with CC smoke. The aerosol was chemically analyzed confirming that none of the determined HPHCs in the THS 2.2 were increased compared to the CC. 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 are given in the Investigator's' Brochure (PMI, 2013a).

Several clinical studies have been conducted on THS 1.0, 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.

The previous version of THS 2.2, namely THS 2.1 was tested in two exploratory clinical studies to measure the nicotine plasma kinetic profile (PK) (clinical trial.gov identifier: NCT01780688) and to assess the reduction of exposure to HPHCs (clinical trial dot. gov identifier: NCT01780714) when switching from CC to THS 2.1. 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. Clinical studies conducted so far revealed no safety concern for either of the previous version of THS 2.2 tested. Further details on the clinical data are provided in the Investigators' Brochure (PMI, 2013a).

## 2.2 Purpose of the Study

The overall goal of the study is to show that the *ad libitum* use of THS 2.2 for 5 days by adult healthy smokers results in a reduction in selected BoExp to HPHCs (except BoExp to nicotine) in a well-controlled environment and to obtain information about safety in subjects using the THS 2.2 product as compared to smokers continuing smoking their own preferred brand of CC. Smokers who are asked to abstain from using any nicotine/tobacco containing products will be used as a reference point to THS 2.2 to evaluate how similar is the reduced exposure in the THS 2.2 arm as compared to smoking abstinence. The subjects allocated to the THS 2.2 and CC arms will be allowed to use their assigned product *ad libitum*.

Additional parameters will be explored on selected variables (e.g., Cytochrome P450 2A6 [CYP2A6]/Cytochrome P450 1A2 [CYP1A2] enzymatic activity, pharmacokinetic [PK] profile of nicotine and cotinine, product evaluation, product use and related subjective effects, human smoking topography [HST], and selected risk markers).

## 2.3 Anticipated Benefits and Risks

### 2.3.1 Anticipated Benefits

Research conducted by the United Kingdom (UK) National Health Service has shown that up to 75% of smokers want to quit. Despite associated health risks, however, only 2% of smokers make a smoking cessation attempt each year. Advice on health risks associated with smoking and smoking cessation will be provided at Screening, at Admission, and at the Day of Discharge. 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 and without 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/CC)

- 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 SA 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 objective of this study is:

- To demonstrate the reduction of primary biomarkers of exposure (BoExp) in smokers switching from conventional cigarettes (CC) to THS 2.2 as compared to smokers continuing to smoke CC.

## 3.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To determine the levels of nicotine on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.
- To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to smoking abstinence (SA).
- To describe the pharmacokinetic profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To describe the changes in Cytochrome P450 1A2 enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.
- To describe the daily THS  Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
- To monitor the safety profile during the study.

## 3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and smokers switching from CC to SA:
    - Excretion of mutagenic material in urine.

- Subjective effects of smoking.
- CYP2A6 activity, and
- Selected risk markers.

- To evaluate in smokers switching from CC to THS 2.2, smokers continuing to smoke CC and smokers switching from CC to SA the relationship between:
  - Nicotine equivalents (NEQ) and primary and secondary BoExp.
  - Selected risk markers and primary, secondary BoExp, and NEQ.

- To describe the following parameters over the course of the study in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:
  - Product evaluation.
  - Smoking pattern.

- To describe the following parameter over the course of the study in smokers switching from CC to THS 2.2:
  - Potential combustion occurrences in tobacco plugs.
  - Filter analysis.

## 3.4 Study Endpoints

The primary and secondary BoExp measured in this study are presented in Table S1.

Table S1:

| | **Biomarkers of Exposure (BoExp)** | **HPHCs** | **Matrix** |
|---|---|---|---|
| Primary BoExp | monohydroxybutenyl mercapturic 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 |
| Secondary BoExp | carbon monoxide | CO | Exhaled breath |
| | total 1-hydroxypyrene (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-hydroxyethyl mercapturic acid (HEMA) | ethylene oxide | Urine |
| | 3-hydroxy(a)benzopyrene | benzo(a)pyrene | Urine |
| | 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) | crotonaldehyde | Urine |
| | S-benzylmercapturic acid (S-BMA) | toluene | Urine |
| | total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) | Urine |
| BoExp to nicotine | NEQ<br>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 in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.
    - Monohydroxybutenyl mercapturic acid, 3-hydroxypropylmercapturic acid, S-phenylmercapturic acid (concentration adjusted to creatinine) in 24-hour urine, and carboxyhemoglobin in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

Evaluation Criterion: The study will be considered successful if the study demonstrates a 50% reduction or more for all four primary BoExp in the THS 2.2 arm compared to the CC arm (as measured on Day 5).

### 3.4.2 Secondary Endpoints

- To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

- BoExp listed as secondary (Table S1) for the comparison of levels between smokers switching from CC to THS 2.2 and smokers continuing to smoke CC as measured on Day 5 as follows:
  - Carbon monoxide (CO) (expressed as ppm) in exhaled breath.
  - Urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

- To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
  - BoExp listed as primary and secondary (Table S1) for the comparison of levels between smokers switching from CC to THS 2.2 and smokers continuing to smoke CC as measured from Day 1 to Day 5.
    - 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 on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.
    - NEQ (expressed in quantity excreted and concentration adjusted to creatinine) (Table S1) in 24-hour urine on Day 5 and from Day 1 to Day 5.
    - Nicotine and cotinine in plasma on Day 5 and from Day 1 to Day 5.

- To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to SA.
  - BoExp listed as primary and secondary (Table S1) from Day 1 to Day 5 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 describe the PK profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.
    - Peak (highest concentration value along the day) on Day 5 in plasma.
    - 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 changes in CYP1A2 enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.
    - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5.

- To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:
    - Number of Tobacco Sticks and CC used each day for each subject from Day 1 to Day 5.

- To monitor the safety profile during the study:
    - AEs/ SAEs and device events including THS 2.2 malfunction/misuse.
    - Respiratory symptoms: cough assessment by visual analogue scale (VAS), Likert scales, and one open question.
    - Vital signs.
    - Spirometry.
    - Electrocardiogram (ECG).
    - Clinical chemistry, hematology, and urine analysis safety panel.
    - Physical examination.
    - Concomitant medication.

### 3.4.3 Exploratory Endpoints

- To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to smokers switching from CC to SA:
    - Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 in 24-hour urine.

- Subjective effects of smoking: Questionnaire of Smoking Urges (brief version) (QSU-brief); Minnesota Nicotine Withdrawal Scale, revised version on Day 5.
- CYP2A6 enzymatic activity: in plasma on Day 6, using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.
- Selected risk markers: 8-epi-prostaglandine F2α (8-epi-PGF2α) and 11-dehydro-thromboxane B2 (11-DTX-B2) measured in 24-hour urine on Day 5.

- To evaluate in smokers switching from CC to THS 2.2, smokers continuing to smoke CC, and smokers switching from CC to SA the relationship between:
  - NEQ and primary and secondary BoExp in 24-hour urine on Day 5.
  - Primary, secondary BoExp, NEQ and risk markers (8-epi-PGF2α and 11-DTX-B2) in 24-hour urine.

- To describe the following parameters over the course of the study in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:
  - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
  - 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 CC to THS 2.2:
  - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
  - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm.

# 4 INVESTIGATIONAL PLAN

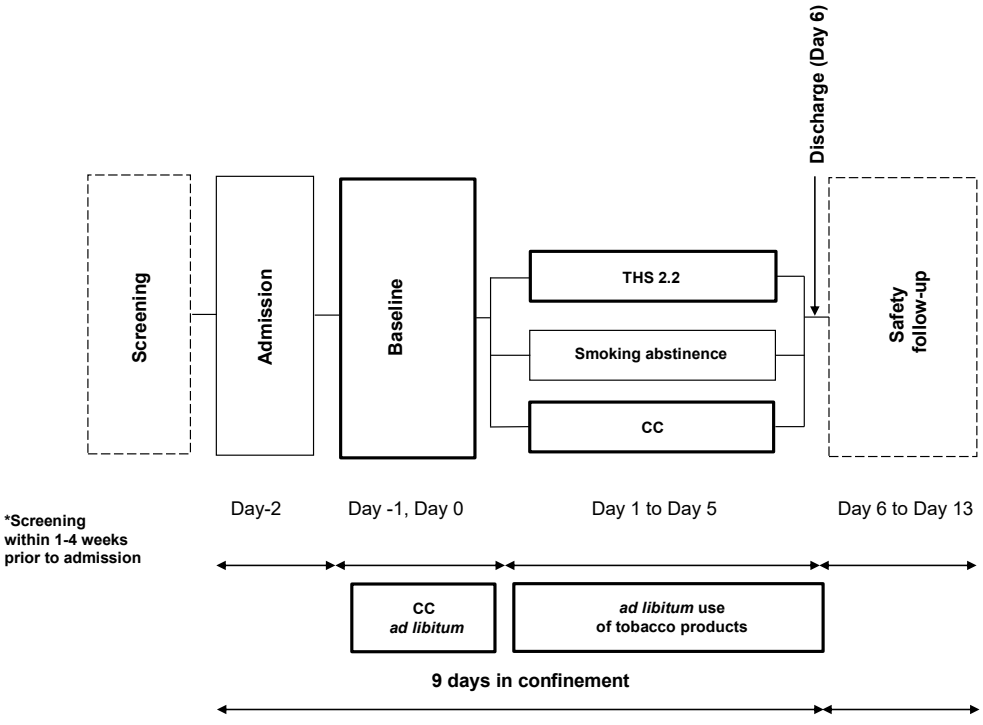
## 4.1 Overall Study Design and Plan

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

This is an *ad libitum* smoking study. In general, smoking during confinement will be allowed between 06:30 AM and 11:00 PM.

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 and CC in the THS 2.2 and CC arms respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each Tobacco Stick/CC on demand of the subject.

Figure S1: Study Design




Abbreviations: THS 2.2 = Tobacco Heating System 2.2; CC = conventional cigarettes.

- Screening period over 4 weeks (Day -30 to Day -3) prior to admission to the clinic (Day -2):

  A demonstration of the THS 2.2 product will be done by the site staff during the Screening Visit. Subjects will be in a confinement setting for 9 days from Day -2 onwards. Screening procedures do not necessarily have to be conducted on the same day.

- 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 (use of up to 3 THS Tobacco Sticks). In female subjects, the THS 2.2 product test may 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.

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

  All subjects will continue smoking their single preferred brand of CC and baseline values will be recorded. On Day 0, subjects will be randomized to one of the 3 study arms in a 2:1:1 ratio using a stratified randomization:

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

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

- Exposure period (from Day 1, 06:30 AM until Day 5, 11:00 PM):

  The exposure period will consist of 5 days of ad libitum use of the assigned product between 06:30 AM and 11:00 PM in THS 2.2 and CC arms. Use of any tobacco/nicotine-containing product other than the assigned product will not be allowed and may, at the discretion of the Investigator or designee, result in the subject withdrawal from the study.

  Subjects in the SA arm will be asked to abstain from smoking any nicotine/tobacco-containing product and will not be provided with medication to support SA.

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

- Day of Discharge (Day 6) (from Day 5, 11:01 PM to time of Discharge):

  Procedures of Discharge, including but not limited to laboratory parameters, will be conducted to discharge the subject from the clinic after 9 days in a confined setting. Use of CC will be allowed on Day 6, but only after spirometry has been performed.

- Safety follow-up period (from Day 6, time of Discharge to Day 13):

After time of Discharge, subject will enter a 7-day safety follow-up 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 actively followed until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found. The end of study (EOS) is defined as the time of Discharge on Day 6 plus 7-day follow-up period.
During the study, subjects in the CC and THS 2.2 arms who want to quit smoking will receive appropriate medical advice and will be referred to a smoking cessation councilor.

## 4.2 Rationale for Study Design and Control Groups

This clinical study aims to demonstrate reduction in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2, a candidate MRTP (see IB, **Error! Reference source not found.**).

The main reference product in this study will be smokers who continue to smoke CC. Smokers who stop smoking (the SA arm) will be used as a reference point.

The exposure period in confinement will provide information on exposure reductions in a well-controlled environment and will allow full control of daily CC consumption. The choice of HPHCs to be assessed in this study is derived from the WHO (Ashley et al, 2008) and the draft guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke (Food and Drug Administration, 2012b).

In the WHO list, 9 HPHCs (acrolein, CO, 1-3 butadiene, benzene, N-nitrosonornicotine [NNN], 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [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 9 priority HPHCs will be assessed by measuring their respective BoExp as primary endpoints after 5 days of exclusive use of THS 2.2, CC, 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 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 tested candidate MRTP for 5 days, similarly to that observed in smokers who stopped smoking (data on file from a previous study.

In addition to the 9 HPHCs recommended to be measured by WHO list, the FDA has required an additional 9 HPHCs for reporting to FDA (in total 18 HPHCs in cigarette smoke) (Food and Drug Administration, 2012b). From the WHO and FDA list, exposure to additional 9 HPHCs ( acrylonitrile, 4-aminobiphenyl [4-ABP], 1-aminonaphthalene [1-NA], 2-aminonaphthalene [2-NA], benzo[a]pyrene, crotonaldehyde, NNK, NNN, and toluene) will be assessed by measuring the respective BoExp as secondary endpoints after 5 days of exclusive use of THS 2.2, CC, or SA.

Cytochrome P450 1A2 activity, which is well known to be increased by smoking and to be decreased upon SA, will be measured in this study to evaluate the effect of THS 2.2 use on the activity of this enzyme (Faber and Fuhr, 2004) and data on file from a previous study (PMI, 2009).

Additional risk markers will be assessed in this study as exploratory endpoints to understand if the reduced exposure results in biological changes. The risk markers have been selected based on their changes shown in smoking cessation studies as well as their believed association to health risks. The risk markers are:

- Prostaglandin 8-epi-PGF2α is a well-established marker of oxidative stress, a pathway which is involved in atherosclerosis. F2-isoprostanes are bioactive prostaglandin-like compounds that are produced from arachidonic acid through a non-enzymatic process of lipid peroxidation catalyzed by oxygen free-radicals. On smoking cessation, the level of 8-epi-PGF2α decreases rapidly within 1 to 2 weeks to the levels seen in non-smoker plasma, serum, and urine (Pilz et al, 2000).
- 11-DTX-B2 (a major stable metabolite of thromboxane A2, which elicits mainly platelet aggregation). This risk marker was reported to decrease upon smoking cessation (Benowitz et al, 1993, Morita et al, 2005).

All subjects will be asked to provide their own CC 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 used questionnaires, except the cough and HST questionnaires, are either available as a validated questionnaire in the local language or will be forward-translated and back-translated with subsequent independent verification.

## 4.4 Study Duration

The entire study duration per subject will be 17 to 44 days, including a Screening period of up to 4 weeks days prior to baseline (Day -30 to Day -3), a 9-day confinement period (afternoon of Day -2 to time of Discharge at Day 6), followed by a 7-day safety follow-up period (until Day 13) for the recording of spontaneously reported new AEs/SAEs, and the follow-up of ongoing AEs/SAEs by the site.

The 9-day confinement period consists of:

- The run-in period: defined as from the admission to the clinic until 06:29 AM of Day -1.
- The baseline period: defined as 06:30 AM at Day -1 until 06:29 AM of Day 1.
- The 5-day exposure period during confinement: defined as from 06:30 AM of Day 1 until 11:00 PM of Day 5.
- The Day of Discharge defined as (Day 6) (from Day 5, 11:01 PM to time of discharge).

# 5 STUDY POPULATION

## 5.1 Selection of Study Population

In total, 160 female or male smoking, but healthy Caucasian subjects who smoke per day at least 10 non-menthol CC 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. The maximum number of CC is not limited. Subjects must have a smoking history of at least 3 years of consecutive smoking prior to the Screening Visit. There will be no brand restrictions. Subjects can smoke different non-menthol brands until Admission to the clinic. From Admission to the clinic onwards, however, they must restrict themselves to one preferred, non-menthol CC brand. The smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/ml). Each sex and each of the smoking strata should have a quota applied to ensure they represent at least 40% of the study 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 21 to 65 years (inclusive). | Safety | X | |
| 3. Subject is of Caucasian origin. | Effect | X | |
| 4. Smoking, but healthy subject as judged by the Investigator or designee based on all available assessments from the Screening period/Day of Admission (e.g., safety laboratory*, spirometry* Forced expiratory volume in 1 second [($FEV_1$) / Forced vital capacity (FVC) >0.7 at post-bronchodilator spirometry, post-bronchodilator $FEV_1$ >80% predicted value, and | Safety | X | X |

| Inclusion Criteria | Rationale | Screening | Day of Admission (Day -2) |
|---|---|---|---|
| post-bronchodilator FVC >80% predicted value], vital signs, physical examination, electrocardiogram [ECG], chest X-ray, and medical history). | | | |
| 5. Subject is a current smoker (based on self-reporting), who for the last 4 weeks has smoked at least 10 commercially available non-menthol CCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO per cigarette, as labeled on the cigarette package. Furthermore, the subject has smoked for at least the last 3 consecutive years. The smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/ml). | Effect | X | X |
| 6. The subject is a current smoker who does not plan to quit smoking in the next 3 months. | Safety | X | |
| 7. The subject is ready to accept 5 days of SA. | Safety | X | X |
| 8. The subject is ready to accept using the THS 2.2 product. | Effect | | X |

* Safety laboratory and spirometry with bronchodilator will be used for eligibility at screening only

### 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 or designee 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, subject in a social or sanitary establishment, prisoners or subjects who are involuntarily incarcerated). | Administrative | X | |
| 3. The subject has a 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 or designee. | Safety | X | X |
| 4. The subject has a body mass index (BMI) <18.5 or ≥32 kg/$m^2$. | Safety | X | X |
| 5. As per Investigator or designee judgment, the subject has medical conditions which require or will | Effect | X | X |

| Exclusion Criteria | Rationale | Screening | Day of Admission (Day -2) |
|---|---|---|---|
| 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 CC (either tobacco-based products or nicotine replacement therapy [NRT]) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment. | Effect | X | X |
| 7. The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug (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 or designee if these can potentially interfere with the study objectives or subject's safety. | Effect | X | X |
| 9. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid. | Effect | X | X |
| 10. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere | Administrative | X | X |

| Exclusion Criteria | Rationale | Screening | Day of Admission (Day -2) |
|---|---|---|---|
| with the subject's participation in the study. | | | |
| 11. The subject has a positive urine drug test. | Administrative | X | X |
| 12. Positive serology test for human immunodeficiency virus (HIV)1/2, hepatitis B surface antigen (HbsAg), or hepatitis C virus (HCV). | 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, or 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, or 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:<br>Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding. | Safety | X | X |

| Exclusion Criteria | Rationale | Screening | Day of Admission (Day -2) |
|---|---|---|---|
| 19. For women only:<br>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 the electronic Case Report Form (eCRF).

When a subject withdraws or is removed from the study, the whole 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. Subject will be informed that the whole examination procedure on Day 6 should be done for their safety but subjects will be free not to do it.

After the time of withdrawal, the subject will enter into the 7-day period of safety follow-up. Subjects withdrawn or removed from the study cannot re-enter the study.

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

- Withdrawal of informed consent.
- Any AE or condition (including clinically relevant changes in a laboratory parameter), at the discretion of the Investigator or designee.
- 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 Investigator or designee terminates the study.
- Withdrawal is considered to be in the best interest of the subject or the other subjects.

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

- Lost to follow-up.

- Concomitant treatment with non-authorized medication as defined in the context of this study (in general, any concomitant medication should be discussed with the Contract Research Organization [CRO] Medical Monitor on an ongoing basis).
- 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 or designee to decide whether or not to withdraw the subject from the study.
- Non-compliance to the study procedures.

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 enrolment and will be replaced by other subjects.

Subjects who violate the entry criteria prior to enrolment, but who were 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 comprises the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable:

| | |
|---|---|
| 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 Tobacco Stick (Tobacco Stick): | The Tobacco Stick (product code C3) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder. |

The overall objective of the product design is to provide an acceptable experience in which the HPHC levels in the aerosol are substantially reduced in comparison with CC.

The THS 2.2 will be provided by the Sponsor.

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

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

**Table 1 Measured aerosol fractions for the THS Tobacco Sticks**

| Constituent (mg/THS Tobacco Stick) | ISO [1] | Health Canada Intense regime [2] |
|---|---|---|
| Tar/NFDPM | 4 | 10.3 |
| Nicotine | 0.5 | 1.32 |
| Carbon monoxide | 1 | 0.6 |

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

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

### 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 non-menthol CC. Subjects are not allowed to roll their own CC.

The reference product to the THS 2.2 during the randomized exposure period is the subject's own preferred commercially available single brand of non-menthol CC.

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

### 6.1.3 Packaging and Labeling

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

Each pack of CC provided by the subject will be labeled to identify which subject the CCs belong to (labels should be affixed to the cellophane wrapper of the lower part of the pack). Each pack of CCs will be labeled to identify necessary information to match the subject with its suppliers.

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

## 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

confinement period, smoking will generally be allowed between 06:30 AM to 11:00 PM. 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.

### 6.2.1 Run-in Period

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

### 6.2.3 Exposure Period

Subjects will not be allowed to smoke any CC or use any nicotine/tobacco-containing products other than their assigned product/regimen.

#### 6.2.3.1 THS 2.2 Arm

Subjects randomized to the THS 2.2 arm will use exclusively THS 2.2 from Day 1, 06:30 AM onwards until Day 5, 11:00 PM.

#### 6.2.3.2 Conventional Cigarette Arm

Subjects randomized to the CC arm will continue smoking their CC from Day 1, 06:30 AM onwards until Day 5, 11:00 PM.

#### 6.2.3.3 Smoking Abstinence Arm

Subjects randomized to the SA study arm will be instructed to abstain from smoking from Day 1, 06:30 AM onwards until Day 5, 11:00 PM. They will not be provided with medication supportive for smoking abstinence.

### 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 or designee.

### 6.2.5 Safety Follow-up Period

During the safety follow-up period (after discharge at Day 6 until Day 13), all subjects are free to smoke their own CC *ad libitum*. Subjects in the SA arm, who wish to continue their SA, or any subject who wish to stop smoking 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.

## 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 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 3 study arms: THS 2.2:CC:SA in a 2:1:1 ratio. Stratified randomization will be conducted by sex and by average daily CC consumption in the 4 weeks prior to the Screening Visit as reported by the subject (those smoking 10 to 19 CC and those smoking >19 CC per day). 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 Investigators or designees 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. |

Abbreviations: CRO = Contract Research Organization; PMI = Philip Morris International.

(*) 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, each CC will be dispensed to the subjects. Subjects in the THS 2.2 arm will be provided by the site personnel with Tobacco Sticks from Day 1 to Day 5. One CC/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 (CC/THS 2.2) use has to be documented from Day -1 for CC and from Day 1 for Tobacco Sticks onwards. The subject must not take a puff of the Tobacco Stick during the pre-heating time. The product will not be promoted for commercial distribution or test market.

### 6.5.2 Storage and Accountability

The THS 2.2 and CC 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 staff. Subjects will return each butt of CC and any used Tobacco Stick immediately after use. This will be documented in appropriate log.

The filters and tobacco plugs of all used Tobacco Sticks will be collected from Day 1 to Day 5, using dedicated vials for accountability and subsequent analysis of both nicotine and tar assessments in the filters and identification of potential combustion occurrences in the tobacco plugs.

### 6.5.3 Investigational Product Retention

The study site will destroy or return to the Sponsor any unused Tobacco Sticks and will return to the Sponsor the THS 2.2 product components upon study completion.

Irrespective of the study arm on the time of Discharge from the clinic, the site staff will return to the subjects any remaining CCs given by them on the Day of Admission.

### 6.5.4 Compliance to Investigational Product(s)

Compliance for all study arms will be ensured by strict distribution of the products (product by product) and collection of Tobacco Sticks, and CC butts will be documented in appropriate log.

In addition, in the SA arm, compliance will be chemically verified using an exhaled CO breath test. The cut-off point for the CO breath test value to distinguish tobacco use vs. no tobacco use will be 10 ppm (Benowitz et al, 2002).

## 6.6 Restrictions

### 6.6.1 Smoking Restrictions and Restrictions to the Smoking Abstinence Arm

To avoid cross smoke contamination between the 3 study arms, subjects must use THS 2.2 and CC 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 study arm.

In the THS 2.2 and SA arms, subjects will not be allowed to smoke any CC or use any nicotine/tobacco-containing products (including NRT) from Day 1 (06:30 AM) until Day 5 (11:00 PM). In CC arm, subjects will not be allowed to use THS 2.2, any nicotine/tobacco-containing products and other CCs than collected to the site by the subject.

During the confinement period, smoking will generally only be allowed during the designated smoking times, from 06:30 AM to 11:00 PM. Subjects will not have free access to their CC or THS 2.2; these will be dispensed by the study site staff individually as described in Section 6.5.1.

Smoking will not be allowed during assessments on the Admission Day at the discretion of the site. Smoking will also not be allowed from Day 5, 11:01 PM until the spirometry has been performed on Day 6.

In general, the performance of scheduled procedures has priority over the wish of a subject to smoke. However, this is different on Day 5 due to the assessment of the nicotine profile. If the subject wants to smoke on Day 5 around the time of the blood draw, he/she should inhale/smoke first and the blood will be drawn after the Tobacco Stick/CC has been inhaled/smoked.

### 6.6.2 Dietary Restrictions

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

In order to avoid any effect on assessment of BoExp, grilled or pan-fried meat, pre-cooked meats (e.g., tuna, ham, corned beef, and smoked meats), bacon, and sausage will not be permitted (Smith et al, 1996). 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 and Fuhr, 2004) except when the subject is asked to drink a cup of coffee 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 snacks, 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 8 hours prior to blood draws for the safety laboratory at the Screening Visit, on Day 0, and Day 6,for the serum/plasma bio-banking samples on Day 0 and Day 6, and blood biobanking for transcriptomics (pharmacogenomics) on Day 0 and Day 6.

## 6.7 Concomitant Medication

No medication should be taken during the study from the Screening until the end of the study (time of discharge plus 7-day safety follow-up period) without prior informing the Investigator or designee. However, the 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.

Concomitant use of NSAID and acetylsalicylic acid (including over-the counter products) is not allowed, as all of them could interfere with the levels of 11-DTX-B2 and possibly other risk markers. 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 2 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 eCRF (for details, see Section 6.7). Concomitant medications should be followed-up with the CRO Medical Monitor on an ongoing basis.

The drugs and substances shown in Table 2 are a selection of drugs considered to have an impact on CYP1A2 and/or CYP2A6 activity (Chang and Kam, 1999; Ingelman-Sundberg et al, 1999; Lacy et al, 2007). Prior to database lock, 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 14 days 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. It is at the discretion of the Investigator or designee to assess if the termination of such medication at Screening is medically justified and safe for the subject.

Estrogens for contraception and for hormone replacement therapy, even though known to be CYP1A2 inhibitors, will be allowed in this study. The use of estrogensmust be documented on the eCRF.

**Table 2. Examples of Medications with Effects on CYP1A2 and CYP2A6 Activity**

| Drug name | Substance Class |
|---|---|
| Fluoroquinolones, including ciprofloxacin and ofloxacin, nafcillin, rifampicin | Antibiotic |
| Fluvoxamine, fluoxetine, paroxetine, bupropion, duloxetine, amitriptyline, imipramine, sertraline, mirtazapine, citalopram, thioridazine | Antidepressant |
| Haloperidol, perphenazine, chlorpromazine, propoxyphene fluphenazine, clozapine, olanzapine | Neuroleptic |
| Phenobarbital, primidone, carbamazepine | Antiepileptic |
| Cholorquine, quinidine | Antirheumatic |
| Clotrimazole, terbinafine, fluconazole, ketoconazole, miconazole | Antimycotic |
| Erythromycin, ciprofloxacin, clarithromycin, norfloxacin | Antibiotic |
| Cimetidine, chlorpheniramine, diphenhydramine, ranitidine | H2-receptor antagonist |
| Amiodarone, verapamil, mibefradil, mexiletin, propafenone, propanolol, lidocaine | Antiarrhythmic |
| Losartan, amlodipine, nifedipine, losartan | Antihypertensive |
| Drosperinone, estrogens | Hormonal contraceptives,<br>Agents for hormonal replacement therapy (estrogens) |
| Fluvastatin | Cholesterol-lowering agent |
| Theophylline | Antispasmodic pulmonological agent/Bronchodilator agent |
| Omeprazole, lansoprazole | Proton pump inhibitor |
| Interferon | Antiviral/Immunomodulating agent |
| Methoxsalen | Anti-psoriatic (substance class Furocoumarins) |
| Modafinil, diclofenac, rofecoxib | Analgesic |
| Insulin | Anti-diabetic |
| Sildenafil | Phosphodiesterase-Inhibitor (e.g., used for treatment of Erectile dysfunction) |

| | |
|---|---|
| Quinine | Crystalline alkaloid |
| St. John's Wort | Over-the-counter (herbal remedy) antidepressant |
| Psoralen | Anti-psoriatic (substance class Furocoumarins) |
| Pilocapine | Cholinergic agonists (e.g., used for Glaucoma Therapy) |

Data sources: Chang and Kam, 1999; Ingelman-Sundberg et al, 1999; Lacy et al, 2007. The list is not exhaustive.

The list of drugs provided in Table 2- Examples of Medications with Effects on CYP1A2 and CYP2A6 Activity - is intended to provide guidance for the Investigator or designee; however, should not be considered exhaustive.

# 7 STUDY PROCEDURES

Personnel performing study measurements or recordings must have the appropriate training fully documented. Quality control (QC) 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). Site personnel 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

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

In addition to the ICF/subject information sheet for study participation, the subject will be asked to provide his separate consent for two kinds of biobanking section 1.3 .

- ICF/subject information sheet to the additional bio-banking of serum/plasma/urine samples for further measurements of BoExp and risk markers.
- ICF/subject information sheet 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 providing consent for sample bio-banking. The consent for both bio-banking (for BoExp and risk markers and for transcriptomics 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 and Debriefing

Each subject will be given advice on the risks of smoking 3 times during the study: at the Screening Visit, at Admission (Day -2), and at Day 6. 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 designee, and may additionally be given in a group session.

In addition to the smoking cessation advice, a debriefing of subjects will be done at each smoking cessation advice session to address any intended or unintended beliefs participants have about THS 2.2. 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 by the site staff for possible signs and symptoms of nicotine withdrawal. This includes clinical monitoring, (e.g., vital signs, physical examination, and body weight). It will also involve close monitoring of the subject's behavior, mood, and any AEs. A psychologist may be contacted and will be available upon the subject's request, or if considered necessary, upon the request of the Investigator, designee, or site staff.

## 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 (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 or designee needs to check if inclusion criterion No. 04 is still fulfilled.

### 7.4.1 Demographic Data

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

### 7.4.2 Identification of the Current Cigarette Brand

Identification of the current CC 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 CC brand(s) to the site. On Day -2, subjects will hand their CC supply for the entire confinement period to the site staff. The site staff will document the brand name and yields. A photograph of the front and the side of the CC pack supplied by the subject (bearing the tar, nicotine, and CO yields) will be taken by the study site staff in addition to recording the brand name and yields. 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 Disc [CD]).

### 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 3 consecutive years, to determine the number of CC smoked during the previous 4 weeks, and to evaluate if the CCs smoked during the previous 4 weeks were non-menthol CCs. 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 CC (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 willing to abstain from smoking for at least 5 days (as required in the study protocol inclusion criteria). 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 Product Test of the THS 2.2

All subjects will be shown a demonstration of the THS 2.2 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 product (use of up to 3 THS Tobacco Sticks).

In female subjects, the THS 2.2 product test may 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 those subjects who are willing and able to use the product can participate in the study. The product test will be the last assessment prior to enrolment.

### 7.4.5 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical history as well as any concomitant diseases will be documented at the Screening Visit. Medical history is defined as any condition that started 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 within 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 captured in the eCRF.

### 7.4.6 Physical Examination

A physical examination will be conducted at the Screening Visit, at Admission (Day -2), and at Day 6.

Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

### 7.4.7 Body Height and Weight

Body weight will be recorded at all time points at the Screening Visit, at Admission (Day -2), and at Discharge on at Day 6. Body height will be measured only at the Screening Visit.

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

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

### 7.4.8 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured at the Screening Visit, at Admission (Day -2), and in the morning of every day of the confinement period (i.e., Day -1 to Day 6). 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.

### 7.4.9 Other Clinical Assessments

#### 7.4.9.1 Spirometry

Spirometry with and without a short-acting bronchodilator will be done at the Screening Visit to evaluate inclusion/exclusion criteria (the post-bronchodilator results). At screening, spirometry without bronchodilator will be done first, and then, spirometry with bronchodilator. Furthermore, spirometry without bronchodilator will be performed at Day 0 (baseline values), and at Day 6 (for comparison with the baseline values). Spirometry has to be done prior to smoking the first CC of the day on Day 0 and Day 6.

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 National Health and Nutrition Examination Survey III predicted set.

All personnel performing lung function testing should have the appropriate training and 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.

#### 7.4.9.2 Electrocardiogram

An ECG will be recorded at Screening and at Day 6. Electrocardiogram 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 QT 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 in 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.

#### 7.4.9.3 Chest X-ray

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

## 7.5 Biomarker Assessment

All bioanalytical assays and laboratory assessments 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 nicotine or CO.

### 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 CO in all 3 study arms. The 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 (see Section 6.5.4).

*Carbon Monoxide Breath Test*

Carbon monoxide in exhaled breath will be measured using the Smokerlyzer® e.g. Micro+™ Smokerlyzer® or similar device.

On Days -1 to Day 5, the CO breath test will be conducted 4 times per day. The first test should be conducted within 15 minutes prior to the first product use. The other 3 tests should be conducted as defined in section 9.

On Days 1 to Day 5, for subjects in the SA arm, the first CO breath test will be done between 08:00 AM and 10:00 AM. The other 3 tests should be conducted as defined in section 9.

On Day -2 and Day 6, the CO breath tests will be conducted once.

*Carboxyhemoglobin*

Assessment for COHb will be performed at the local laboratory. Carboxyhemoglobin in blood will be assessed on a daily basis, starting from Day -1 until Day 5.

On Day -1 to Day 4: one blood sample as defined in section 9.

On Day 5: one blood sample will be collected within 15 minutes prior to the first product use. The three other blood sample will be collected as defined in section 9.

For subjects in the SA arm, the first COHb will be done between 08:00 AM-10:00 AM. The three other blood samples will be collected as defined in section 9.

#### 7.5.1.2 Plasma Nicotine and Cotinine

Nicotine and cotinine concentrations will be measured in plasma to evaluate the exposure to nicotine. For subjects in the SA arm, blood samples will be collected on Day 0 to Day 4, at comparable time points. No nicotine PK profile will be done for subjects in the SA arm on Day 5 and Day 6.

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

One blood sample for nicotine and cotinine will be drawn each day 08:00 PM-10:00 PM.

- Nicotine/cotinine PK profile on Day 5 and Day 6 (THS 2.2 and CC arms only):

In total, 9 blood samples will be drawn on Day 5. The first blood sample on Day 5 will be drawn within 15 minutes prior to the first product use (T0). On Day 5, T0 will serve as a reference for the time to peak concentration. An additional 8 blood samples will be drawn in 2 hour intervals after T0. The last blood sample should be drawn no later than 11:00 PM, corresponding to the end of the product use. At all time points, if the subject wants to smoke around the time of the blood draw, he/she should smoke first and the blood will be drawn after the product has been used. Depending on the time of the first product use, it may be that fewer than 8 blood samples will be collected from a subject after T0.

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).

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

On Day 5, one blood sample will be drawn 08:00 PM-10:00 PM.

On Day 6, one blood sample will be drawn 08:00 AM-10:00 AM.

#### 7.5.1.3 Other Biomarkers of Exposure

The following BoExp will be measured in 24-hour urine collection samples as per the Schedule of Events (Appendix 1):

- Primary BoExp: MHBMA, 3-HPMA, S-PMA.
- Secondary BoExp: total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 1-NA, total 1-hydroxypyrene (1-OHP), total NNN, 3-hydroxy(a)benzopyrene, 4-ABP, 2-NA, o-toluidine (o-tol), NEQ, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), S-benzylmercapturic acid (S-BMA), and 3-hydroxy-1-methylpropylmercapturic acid (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 recorded/measured at the following time points:

- 8-epi-PGF2α to be measured in 24-hour urine on Day 0 and Day 5.
- 11-DTX-B2 to be measured in 24-hour urine on Day 0 and Day 5.

#### 7.5.2.2 CYP1A2 Activity test

Cytochrome P450 1A2 activity will be measured at Day 0 and at Day 5. Measurement of enzyme activity will be assessed through PX and CAF plasma molar concentrations approximately 6 hours (±15 minutes) after the intake of a cup of coffee made from 4.2 g (±10%) regular instant coffee (Nescafé Gold Instant; Nestlé; Deutschland; CAF content: 72 mg/2 g) with 150 ml ±10 ml water. The CAF content will be approximately 150 mg CAF (Faber and Fuhr, 2004). The exact time of the intake of the cup of coffee in the morning and of the blood sampling (taken 6 hours [±15 minutes] after the intake of the coffee) must be recorded. Cytochrome P450 1A2 activity will be assessed by the measurement of the molar PX/CAF metabolic ratio (Faber and Fuhr, 2004).

#### 7.5.2.3 CYP2A6 activity

Cytochrome P450 2A6 activity will be measured in plasma on Day 0, and on Day 6, using the molar metabolic ratio of *trans*-3'-hydroxycotinine/cotinine (Jacob et al, 2011). Blood sampling for CYP2A6 activity must be done prior to product use.

Cytochrome P450 2A6 activity drives the hepatic 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 and on Day 5 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

### 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, and at Day 6. Blood samples will be taken after at least 8 hours of fasting (see Section 6.6.2). The urine test will be performed semi-quantitatively as a urine dip-stick test. Parameters to be measured are listed in Table 3.

**Table 3. Clinical Laboratory Parameters for Safety Panel**

| Hematology | Clinical Chemistry | Urine analysis |
|---|---|---|
| - Hematocrit (Hct)<br>- Hemoglobin (Hb)<br>- Mean corpuscular hemoglobin (MCH)<br>- Mean corpuscular hemoglobin concentration (MCHC)<br>- Mean corpuscular volume (MCV)<br>- Platelet count<br>- Red blood cell (RBC) count<br>- White blood cell (WBC) count<br>- Differential WBC count:<br>• Neutrophils<br>• Basophils<br>• Eosinophils<br>• Lymphocytes<br>• Monocytes | - Albumin<br>- Total protein<br>- Alkaline phosphatase (AP)<br>- Alanine aminotransferase (ALT)<br>- Aspartate aminotransferase (AST)<br>- Blood urea nitrogen (BUN)<br>- Creatinine<br>- Gamma-glutamyl transferase (GGT)<br>- Fasting Glucose<br>- Lactate dehydrogenase (LDH)<br>- Potassium<br>- Sodium<br>- Total bilirubin<br>- Direct bilirubin<br>- Total cholesterol<br>- Triglycerides | - pH<br>- Bilirubin<br>- Glucose<br>- Nitrite<br>- Red blood cell traces<br>- Protein<br>- Specific gravity |

### 7.6.2 Serology

A test for HbsAg, HCV, and anti-HIV1/2 and p24 antigen will be done at Screening. In case of positive results, the subject will be referred to appropriate medical care.

### 7.6.3 Urine Drug Screen

A urine drug screen will be performed at the 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 dip-stick cotinine test will be performed at Screening and at Admission (Day -2) in order to confirm the subject's smoking status. The test must detect cotinine with a cotinine threshold of ≥200 ng/ml (i.e., One-Step Cotinine Test 008A086, Ultimed, Belgium).

### 7.6.5 Alcohol Breath Test

Subjects will have a breath alcohol test at the Screening Visit and at Admission (Day -2) using an alcometer device (e.g., Alcotest 7410 Plus, Dräger).

### 7.6.6 Urine Pregnancy Testing

All female subjects will undergo pregnancy testing at the Screening Visit, at Admission (Day -2), at Day 6. 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 or designee 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 Sample 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 dip-stick for the safety laboratory, 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 will be 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 Clinical Study Report (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 be around 170 ml, which includes 20 ml for safety and repeated analysis, 20 ml of blood for long-term storage of the biobanking samples for further analysis of biomarkers

of exposure and risk markers (only if additional consents are given, see Section 7.7.3), and 10 ml for long-term storage biobanking samples for further transcriptomics analysis (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 tests, and safety urinalysis.

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. During the sampling period, all urine passed 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 start and the end time of the 24-hour urine collection will be recorded by the study site staff.

For assessment of urine BoExp, creatinine for normalization of urine BoExp, 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, NEQ measured at Day 5 in the 24-hour urine collection starts on Day 5 and ends later on Day 6.

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

### 7.7.3 Long-Term Bio-banking Storage of Blood or Urine

If a subject gives consent for sample bio-banking for BoExp/risk markers, additional samples of urine (from the 24-hour urine collection) and serum/plasma (20 ml of blood total) will be collected.

- Samples from the 24-hour urine will be collected from the urine collections that started on Day 0 and on Day 5, respectively.
- Serum/plasma will be collected on Day 0 and Day 6.

These samples are intended for possible later analysis of additional BoExp/risk markers. No genetic or transcriptogenomics testing will be performed on these samples.

If a subject gives consent for sample bio-banking of whole blood for transcriptomics, a total of 10 ml of blood will be collected to that purpose at Day 0 and Day 6.

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

## 7.8 Other Study Procedures

### 7.8.1 Human Smoking Topography Assessment

Human smoking topography involves the measurement of each smoker's unique way of smoking CCs or using THS 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 4). It consists of a special sample holder (containing a constriction in the middle) which is placed between the subject's mouth and the filter of the CC or THS Tobacco Stick being smoked/used. The sample holder is connected by 2 narrow tubes to a portable data logger/recording system (see Appendix 4 for a description of the device). Any malfunction of the HST SODIM® portable device will be documented in appropriate log.

At Day 0, the HST SODIM® device has to be used for all CC smoked for all subjects. On Day 1 and Day 4 of the confinement period, the HST SODIM® device has to be used for every product use for all subjects in the CC and THS 2.2 arms.

Smoking topography with the HST SODIM® device will not be recorded for subjects smoking CC that are incompatible with the HST SODIM® device (e.g., slim CC).

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 CCs at each cohort but not more than 40 subjects at each cohort.

From Day 1, for subjects in the SA arm, no HST assessments will be performed.

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

#### 7.8.1.1 Human Smoking Topography Parameters:

The HST SODIM® device measures and records the flow and other per-puff parameters listed in Table 4 below. From the per-puff parameters (Table 4), the per-cigarette parameters shown in Table 5 will be derived (representing average values or totals per cigarette).

Prior to calculation of the per-cigarette parameters, the Sponsor's 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 4. 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 5. Human Smoking Topography - Per-Cigarette Parameters**

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

| Description | Variable | Formula | Unit |
|---|---|---|---|
| Total inter puff interval | TIi | Σ Ii | s |
| Average inter puff interval | AvgIi | Σ Qci / NPC, i=1 … NPC | s |
| Total smoking duration | TDFi | Σ DFi | s |
| Total Work | TWi | Σ Wi | mJ |
| Average Work | AvgWi | Σ Wi / NPC, i=1 … NPC | mJ |
| Average pressure drop | AvgPmi | Σ Pmi / NPC, i=1 … NPC | mmWg |
| Average Peak pressure drop | AvgPci | Σ 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) | |

### 7.8.2 THS Filter Analysis

All filters from used Tobacco Sticks will be sent to an external laboratory for analysis.

### 7.8.3 Visual Inspection of THS Tobacco Plugs

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

### 7.8.4 Questionnaires

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

Symptoms or worsening of symptoms 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 or designee 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 site staff, using open, non-directive questions (see Section 8).

#### 7.8.4.1 Fagerström Test for Nicotine Dependence (Revised Version)

Potential nicotine dependence will be assessed at Screening using the Fagerström Test for Nicotine Dependence (FTND) (Fagerström et al, 2012).

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

#### 7.8.4.2 Assessment of Cough

Subjects will be asked to assess the respiratory symptom 'cough' on a VAS, on 3 Likert scales, and with an open question on a daily basis during the confinement period from Day 0 to Day 6. On each day, cough assessment has to be done prior to product use.

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, 3 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 staff about their coughing.

#### 7.8.4.3 Modified Cigarette Evaluation Questionnaire

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

- Smoking satisfaction (satisfying, tastes good, 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).

Only subjects who are randomized to the THS 2.2 and CC arms will complete this questionnaire. The subjects will complete the questionnaire by themselves.

The MCEQ will be completed by subjects during the confinement period from Day -1 to Day 5.

#### 7.8.4.4 Questionnaire of Smoking Urges brief version

To assess the urge-to-smoke, all subjects will be asked to fill-in a 10-item brief version of the QSU-brief (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.

#### 7.8.4.5 Minnesota Nicotine Dependence/Withdrawal Scale (revised version)

The MNWS is a valid and reliable scale that has been used previously to examine signs and symptoms of withdrawal from cigarette smoking (Hughes and Hatsukami, 1986; Hughes and Hatsukami, 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. On each day, MNWS has to be asked prior to product use.

#### 7.8.4.6 Human Smoking Topography Questionnaire

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

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

- The end of the baseline period on Day 0 for all subjects smoking CC compatible with the HST SODIM® device (i.e., non-slim CC).
- On Day 4 for all subjects in the THS 2.2 and for all subjects smoking CC compatible with the HST SODIM® device (i.e., non-slim CC).

# 8 ADVERSE EVENTS

## 8.1 Definitions

### 8.1.1 Adverse Events

The FDA MRTP guidelines specify the following definition for AEs 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 by 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 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/subject information sheet will not be recorded as SAEs, however, they will be recorded as AEs only. Any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

## 8.2 Assessment of Adverse Events

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

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

For each AE, the intensity will be graded on a 3-point intensity scale (mild, moderate, severe) using the definitions provided in Section 8.2.5.

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 eCRF and on a separate SAE report form (see Section 8.3).

### 8.2.2 Period of Collection

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

### 8.2.3 Screening Period

During the Screening period, all AEs will be actively collected by the study site staff as described in this document.

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 assessed by the Investigator or designee in order to establish relationship or relatedness in respect to the product or study procedures. Only the product-related AEs and the study procedures-related AEs will be captured for further reporting in accordance with respective regulatory guidelines.

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.

### 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 site staff.

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

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

At the end of the safety follow-up period all ongoing AEs/SAEs will be followed up by the Investigator or designee 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 or designee 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 or designee 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 or designee 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 and Follow-Up of Serious Adverse Events

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

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

| | | |
|---|---|---|
| [redacted]**:** | **Phone number:** | [redacted] |
| | **Fax number** | [redacted] |
| | **E-mail:** | [redacted] |
| | **Address:** | [redacted] |
| **Sponsor:** Contact: [redacted] MD, Medical Safety Officer | **Phone number:** | [redacted] |
| | **E-mail:** | [redacted]@pmi.com |
| | **Address:** | Philip Morris Products S.A.<br>R&D Innovation Cube<br>Quai Jeanrenaud 5 |

2000 Neuchâtel
Switzerland

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

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

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

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

The SAE report form to be used in this study is provided as a separate document. All SAEs will be recorded on the eCRF, 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 or designee and assessed for clinical relevance. If the Investigator or designee 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 the Common Terminology Criteria for Adverse Event and Common Toxicity Criteria [CTCAE] version 4.03) will be used by the Investigator or designee to assess abnormal laboratory AEs as follows:

- All Grade 1 abnormal laboratory values will be evaluated by the Investigator or designee with respect to baseline value and clinical relevance. If considered to be clinically relevant, the Investigator or designee 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 or designee 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 or designee must report this worsening as an AE.

- Where there is no grading available, the abnormal laboratory value will be evaluated by the Investigator or designee, and assessed for clinical relevance. If considered to be clinically relevant, the Investigator or designee 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 or designee, be reviewed and assessed. Even if they do not meet the criteria of the CTCAE grading scheme (please see above), the Investigator or designee may consider them to be of clinical relevance and, if they are, must report them as AEs.
- In general, laboratory values will be recorded as 'increased <lab parameter>' or 'decreased <lab parameter>' to ensure consistency of recording/coding.

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

## 8.5 Reporting and Follow-Up of Pregnancies

For pregnancies detected during the Screening period and prior to first THS 2.2 use, the subject will be considered as a screening failure and removed from the study. No Pregnancy Form will be completed, however, the diagnosed pregnancy must be captured in the Screen Failure eCRF.

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

Any pregnancy potentially associated to exposure to the IP, including pregnancies spontaneously reported to the Investigator or designee after the EOS must be reported by the Investigator or designee 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 or designee will complete a Pregnancy Form (provided as a separate document) for all pregnancies diagnosed (including positive urine pregnancy tests).

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

[redacted] will follow-up pregnancies only if they were detected after first product use (i.e., after THS 2.2 product 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 Investigator or designee is responsible for informing the IEC 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 procedures as described for the Day of Discharge, as soon as possible and will enter the period of safety follow-up. The Investigator or designee and/or [redacted] will follow-up these AEs until they have resolved, stabilized (i.e., no worsening of condition), or an acceptable explanation has been found.

## 8.7 Investigational Device Misuse

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

Investigational device misuse may result in use-related hazards.

Use-related hazards are derived from the US Food and Drug Administration Medical Device Use-Safety Guidance (Food and Drug Administration, 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 device, etc.) that result in hazards must be documented and reported by the Investigator or designee".

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

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

## 8.8 Investigational Device Malfunction

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

Furthermore, any malfunctions of the 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 8-hour fasting state for clinical laboratory parameters to be assessed. Table 6 shows the assessments that will be performed at the Screening Visit. First, the ICF/subject information sheet should be given to the subject. When/if the ICF/subject information sheet 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 6. Time Schedule - Screening Visit**

| Time (Day-30 to Day-3) | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Screening** | |
| | | Informed consent/Subject Information Sheet and Informed consents/subject information sheets for the two bio-banking | |
| | | Advice on the risk of smoking and debriefing | |
| | | Demographic data collected | |
| | | Identification of current CC brand | |
| | | Medical history/concomitant disease | |
| | | Prior medication (4 weeks prior to Screening Visit) and concomitant medication | |
| | | Smoking history | |

| Time (Day-30 to Day-3) | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Screening** | |
| | | Willingness to quit smoking within the next 3 months and to abstain from smoking for at least 5 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 8 hours of fasting |
| | √ | HIV, hepatitis B and C | |
| | | Physical examination and height, weight, calculation of BMI | |
| | | THS 2.2 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 | |
| | | Urine pregnancy test (all females) | |
| | | FTND | |
| | | Spirometry without short-acting bronchodilator first, and then with | 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; CC = conventional cigarette(s); ECG = electrocardiogram; FTND = Fagerström Test for Nicotine Dependence; HIV = human immunodeficiency virus; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2.

## 9.2 Confinement Period (Days -2 to Day 6)

### 9.2.1 Admission (Day -2)

The procedures of Day -2 can be performed in order deemed most practical except product test which will be the last assessment prior to enrolment after all eligibility criteria have been met. Table 7 shows the assessments that will be performed at Admission (Day -2):

**Table 7. Time Schedule - Day -2**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Admission** | |
| | | AE/SAE recording; concomitant medication, | All day |
| | | Urine pregnancy test (all females only) | |
| | | Advice on the risk of smoking and debriefing | |
| | | Smoking history | |
| | | Willingness to abstain from smoking for at least 5 days | |
| | | Urine drug screen | |
| | | Urine cotinine screening test | |
| | | Alcohol breath test screen | |
| | | CO breath test | |
| | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| | | Physical examination, weight, BMI | |
| | | Inclusion/exclusion criteria | |
| | | Identification of current CC brand and picture | |
| | | THS 2.2 product test | |
| Until 11:00 PM | | Smoking Period | |
| In the evening until 09:00 PM | | Dinner | |
| | | Enrolment | Only after all eligibility criteria have been met |
| 11:00 PM | | End of study day | |

Abbreviations: AE = adverse event; BMI = body mass index; CC = conventional cigarette(s); CO = carbon monoxide; SAE: serious adverse event; THS 2.2= Tobacco Heating System 2.2.

### 9.2.2 Baseline Period (Day -1 to Day 0)

Table 8 and Table 9 show the assessments that will be performed at baseline (Day -1 and Day 0, respectively).

The start times given are for the first subject. All subsequent subjects should complete procedures within the time window given in the tables.

**Table 8. Time Schedule - Day -1**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Baseline Day -1** | |
| | | AE/SAE recording; concomitant medication | All day |
| 06:30 AM+/- 30min | | Start urine collection to Day -1 sampling bottle | |
| | | CO breath test | To be done within 15 minutes prior to smoking |
| 06:30 AM | | Beginning of smoking period | |
| Before 10:00 AM | | Breakfast | |
| before 12:00 PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| 12:00 PM-02:00 PM | | CO breath test | |
| before 03:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | | CO breath test | |
| Afternoon | | Snacks | |
| In the evening until 09:00 PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |
| 08:00 PM-10:00 PM | √ | COHb in blood | |
| 08:00 PM-11:00 PM | | MCEQ questionnaire , QSU-brief questionnaire | |
| 11:00 PM | | End of smoking period | |

| | | |
|---|---|---|
| 06:30 AM-11:15 PM | Collection of all smoked CC butts | For accountability |

Abbreviations: AE = adverse event; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU-brief = Questionnaire of Smoking Urges (brief version); SAE= serious adverse event; THS 2.2 = Tobacco Heating System 2.2.

**Table 9. Time Schedule - Day 0**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Baseline Day 0** | |
| | | AE/SAE recording; concomitant medication | All day |
| | | Randomization | At any time during the day after eligibility criteria have been met. Subjects are not to be informed of their assigned arm until Day 1. |
| 06:29 AM +/-30 min | | Analysis sample to be taken after final portion of urine has been added to Day -1 sampling bottle. | BoExp and creatinine in 24-hour urine |
| 06:30 AM +/-30 min | | Start of urine collection to Day 0 sampling bottle | |
| | | Assessment of cough (VAS) | To be done prior to smoking but no later than 10:00 PM |
| | | MNWS questionnaire | To be done prior to smoking but no later than 10:00 PM |
| | | Spirometry without short-acting bronchodilator | To be done prior to smoking |
| | √ | CYP2A6 activity in plasma | To be done prior to smoking |
| | | CO breath test | To be done within 15 minutes prior to smoking |
| | | HST | HST SODIM® device has to be used for all product uses if compatible CCs are smoked |
| 06:30 AM | | Beginning of smoking period | |
| | √ | Clinical laboratory parameters (hematology, clinical chemistry) | To be done after at least 8 hours of fasting |
| | √ | Bio-banking for BoExp/ risk markers in serum/plasma (if consent is obtained) | To be done after at least 8 hours of fasting |
| | √ | Bio-banking for transcriptomics (if consent is obtained) | To be done after at least 8 hours of fasting |
| | | Urine safety analysis | |
| Before 10:00 AM | | Breakfast | |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Baseline Day 0** | |
| 10:00 AM-12:00 PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| 10:00 AM-12:00 PM | | A cup of coffee containing approximately 150 mg of CAF | |
| 12:00 PM-02:00 PM | | CO breath test | |
| before 3:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | √ | CYP1A2 activity in plasma | 6 hours +/-15 minutes after intake of cup of coffee |
| 04:00 PM-06:00 PM | | CO breath test | |
| afternoon | | Snacks | |
| In the evening until 09:00 PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |
| 08:00 PM-10:00 PM | √ | COHb in blood | |
| 08:00 PM-10:00 PM | √ | Nicotine, cotinine in plasma | |
| 08:00 PM-11:00 PM | | HST questionnaire | |
| 08:00 PM- 11:00 PM | | MCEQ questionnaire (THS 2.2 and CC arms only),<br>QSU-brief questionnaire | |
| 11:00 PM | | End of smoking period | |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Baseline Day 0** | |
| 6:30 AM-11:15 PM | | Collection of all CC butts | For accountability |

Abbreviations: AE = adverse event; BoExp = biomarkers of exposure; CAF = caffeine; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; CYP2A6 = Cytochrome P450 2A6 HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU-brief = Questionnaire of Smoking Urges (brief version); SAE = serious adverse event; THS 2.2= Tobacco Heating System 2.2; VAS = Visual analogue scale.

### 9.2.3 Exposure Period (Days 1 to 5)

The tables in this section show the assessments that will be performed during the confinement period (Day 1 to Day 5). Table 10 shows the assessments that will be performed on Day 1:

**Table 10. Time Schedule - Day 1**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 1** | |
| | | AE/SAE recording; concomitant medication | All day |
| | | Support during smoking abstinence (SA arm only) if needed | All day |
| 6:29 AM +/-30 min | | Analysis sample to be taken after final portion of urine has been added to Day 0 sampling bottle. Must be prior to first product use of Day 1 | BoExp, creatinine, and Ames mutagenicity in 24-hour urine<br>Risk markers: 8-epi-PGF2α and 11-DTX-B2<br>Bio-banking for BoExp/ risk markers in 24-hour urine (if additional consent is obtained) |
| 6:30 AM +/-30 min | | Start collection to Day 1 sampling bottle | |
| | | Assessment of cough (VAS) | To be done prior to product use but no later than 10:00 PM |
| | | MNWS questionnaire | To be done prior to product use but no later than 10:00 PM |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 1** | |
| | | CO breath test | To be done within 15 minutes prior first product use (for THS 2.2 and CC arms) or 08:00-10:00 AM (SA arm) |
| 6:30 AM | | Beginning of product use | |
| 06:30 AM-11:00 PM | | HST | In THS 2.2 and CC arms, HST SODIM® device has to be used for all product uses if compatible CCs are smoked |
| Before 10:00 AM | | Breakfast | |
| 10:00 AM-12:00 PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| 12:00 PM-02:00 PM | | CO breath test | |
| before 03:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | | CO breath test | |
| afternoon | | Snacks | |
| In the evening before 09:00 PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |
| 08:00 PM-10:00 PM | √ | COHb in blood | |
| 08:00 PM-10:00 PM | √ | Nicotine, cotinine in plasma | |
| 08:00 PM-11:00 PM | | MCEQ questionnaire (THS 2.2 and CC arms only) | |
| | | QSU-brief questionnaire | |
| 11:00 PM | | End of product use | |
| 6:30 AM-11:15 PM | | Collection of all used Tobacco Sticks and smoked CC butts | For accountability |
| | | Collection of all tobacco plugs and filters from all used Tobacco Sticks in dedicated vials | For analysis of combustion occurrences and filter analysis |

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; BoExp = biomarkers of exposure; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU-brief= Questionnaire of Smoking Urges (brief version); SA = smoking abstinence; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2; VAS = visual analogue scale.

Table 11 shows the assessments that will be performed on Day 2 of the confinement period:

**Table 11. Time Schedule - Day 2**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 2** | |
| | | AE/SAE recording; concomitant medication | All day |
| | | Support during smoking abstinence (SA arm only) if needed | All day |
| 6:29 AM +/-30 min | | Analysis sample to be taken after final portion of urine has been added to Day 1 sampling bottle. Must be prior to first product use of Day 2 | BoExp and creatinine in 24-hour urine |
| 6:30 AM +/-30 min | | Start collection to Day 2 sampling bottle | |
| | | MNWS questionnaire | To be done prior to product use but not later than 10:00 AM |
| | | Assessment of cough (VAS) | To be done prior to product use but not later than 10:00 AM |
| | | CO breath test | To be done within 15 minutes prior to first product use (for THS 2.2 and CC arms) or 08:00-10:00 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 12:00PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| 12:00 PM-02:00 PM | | CO breath test | |
| before 03:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | | CO breath test | |
| afternoon | | Snacks | |
| In the evening before 09:00PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |
| 08:00 PM-10:00 PM | √ | COHb in blood | |
| 08:00 PM-10:00 PM | √ | Nicotine, cotinine in plasma | |
| 08:00 PM-11:00 PM | | MCEQ questionnaire (THS 2.2 and CC arms only) | |
| | | QSU-brief questionnaire | |
| 11:00 PM | | End of product use | |
| 6:30 AM-11:15 PM | | Collection of all used Tobacco Sticks and smoked CC butts | For accountability |
| | | Collection of all tobacco plugs and filters from all used Tobacco Sticks in dedicated vials | For analysis of combustion occurrences and filter analysis |

Abbreviations: AE = adverse event; BoExp = biomarkers of exposure; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU-brief = Questionnaire of Smoking Urges (brief version); SA = smoking abstinence; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2; VAS = visual analog scale.

Table 12 shows the assessments that will be performed on Day 3 of the confinement period:

**Table 12. Time Schedule - Day 3**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 3** | |
| | | AE/SAE recording; concomitant medication | All day |
| | | Support during smoking abstinence (SA arm only) if needed | All day |
| 6:29 AM +/-30min | | Analysis sample to be taken after final portion of urine has been added to Day 2 sampling bottle. Must be prior to first product use of Day 3 | BoExp and creatinine in 24-hour urine |
| 6:30 AM +/-30min | | Start collection to Day 3 sampling bottle | |
| | | MNWS questionnaire | To be done prior to product use but not later than 10:00 AM |
| | | Assessment of cough (VAS) | To be done prior to product use but not later than 10:00 AM |
| | | CO breath test | To be done within 15 minutes prior to first product use (for THS 2.2 and CC arms) or 08:00-10:00 AM (SA arm) |
| 6:30 AM | | Beginning of product use | |
| Before 10:00 AM | | Breakfast | |
| 10:00 AM-12:00 PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| 12:00 PM-02:00 PM | | CO breath test | |
| before 03:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | | CO breath test | |
| afternoon | | Snacks | |
| In the evening before 09:00 PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 3** | |
| 08:00 PM-10:00 PM | √ | COHb in blood | |
| 08:00 PM-10:00 PM | √ | Nicotine, cotinine in plasma | |
| 08:00 PM - 11:00 PM | | MCEQ questionnaire (THS 2.2 and CC arms only) | |
| | | QSU-brief questionnaire | |
| 11:00 PM | | End of product use | |
| 6:30 AM-11:15 PM | | Collection of all used Tobacco Sticks and smoked CC butts | For accountability |
| | | Collection of all tobacco plugs and filters from all used Tobacco Sticks in dedicated vials | For analysis of combustion occurrences and filter analysis |

Abbreviations: AE = adverse event; BoExp = biomarkers of exposure; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU-brief = Questionnaire of Smoking Urges (brief version); SA = smoking abstinence; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2; VAS = visual analog scale

Table 13 shows the assessments that will be performed on Day 4 of the confinement period:

**Table 13. Time Schedule - Day 4**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 4** | |
| | | AE/SAE recording; concomitant medication | All day |
| | | Support during smoking abstinence (SA arm only) if needed | All day |
| 6:29 AM +/-30 min | | Analysis sample to be taken after final portion of urine has been added to Day 3 sampling bottle. Must be prior to first product use of Day 4 | BoExp and creatinine in 24-hour urine |
| 6:30 AM +/-30 min | | Start collection to Day 4 sampling bottle | |
| | | Assessment of cough (VAS) | To be done prior to product use but not later than 10:00 AM |
| | | MNWS questionnaire | To be done prior to product use but not later than 10:00 AM |
| | | CO breath test | To be done within 15 minutes prior to first product use (for THS 2.2 and CC arms) or 08:00-10:00 AM (SA arm) |
| 6:30 AM | | Beginning of product use | |
| | | HST | In THS 2.2 and CC arms, HST SODIM® device has to be used for all product uses if compatible CCs are smoked |
| Before 10:00 AM | | Breakfast | |
| 10:00 AM-12:00 PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| 12:00 PM-02:00 PM | | CO breath test | |
| before 03:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | | CO breath test | |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 4** | |
| afternoon | | Snacks | |
| In the evening before 09:00 PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |
| 08:00 PM:10:00 PM | √ | COHb in blood | |
| 08:00 PM:10:00 PM | √ | Nicotine, cotinine in plasma | |
| 08:00 PM-11:00 PM | | HST questionnaire | In THS 2.2 and CC arms only |
| 08:00 PM-11:00 PM | | MCEQ questionnaire (THS 2.2 and CC arms only) | |
| | | QSU-brief questionnaire | |
| 11:00 PM | | End of product use | |
| 6:30 AM-11:15 PM | | Collection of all used Tobacco Sticks and smoked CC butts | For accountability |
| | | Collection of all tobacco plugs and filters from all used Tobacco Sticks in dedicated vials | For analysis of combustion occurrences and filter analysis |

Abbreviations: AE = adverse event;; BoExp = biomarkers of exposure; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU-brief = Questionnaire of Smoking Urges (brief version); SA = smoking abstinence; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2; VAS = visual analog scale.

Table 14 shows the assessments that will be performed on Day 5 of the confinement period:

**Table 14. Time Schedule - Day 5**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 5** | |
| | | AE/SAE recording; concomitant medication | All day |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 5** | |
| | | Support during smoking abstinence (SA arm only) if needed | All day |
| 6:29 AM +/-30 min | | Analysis sample to be taken after final portion of urine has been added to Day 4 sampling bottle. Must be prior to first product use of Day 5 | BoExp and creatinine in 24-hour urine |
| 6:30 AM +/-30 min | | Start collection to Day 5 sampling bottle | |
| | | Assessment of cough (VAS) | To be done prior to product use but not later than 10:00 AM |
| | | MNWS questionnaire | To be done prior to product use but not later than 10:00 AM |
| | | CO breath test | To be done within 15 minutes prior to first product use (for THS 2.2 and CC arms) or 08:00-10:00 AM (SA arm) |
| | √ | COHb in blood | To be done within 15 minutes prior to first product use (for THS 2.2 and CC arms) or 08:00 AM -10:00 AM (SA arm) |
| 6:30 AM | | Beginning of product use | |
| | √ | Nicotine, cotinine in plasma | For THS 2.2 and CC arms: within 15 minutes before first product use (T0): then additional blood samples at 2 hour intervals from T0 until 11:00 PM. Each sample has a time window of +/- 5 minutes<br>For SA arm: at 08:00 PM-10:00 PM |
| Before 10:00 AM | | Breakfast | |
| 10:00 AM-12:00 PM | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 5** | |
| 10:00 AM-12:00 PM | | A cup of coffee containing approximately 150 mg of CAF | |
| 12:00 PM-02:00 PM | | CO breath test | |
| 12:00 PM-02:00 PM | √ | COHb in blood | |
| before 03:00 PM | | Lunch | |
| 04:00 PM-06:00 PM | | CO breath test | |
| 04:00 PM-06:00 PM | √ | COHb in blood | |
| 04:00 PM-06:00 PM | √ | CYP1A2 activity in plasma | 6 hours +/-15 minutes after intake of cup of coffee |
| afternoon | | Snacks | |
| In the evening before 09:00 PM | | Dinner | |
| 08:00 PM-10:00 PM | | CO breath test | |
| 08:00 PM-10:00 PM | √ | COHb in blood | |
| 08:00 PM-11:00 PM | | MCEQ questionnaire (THS 2.2 and CC arms only) | |
| | | QSU-brief questionnaire | |
| 11:00 PM | | End of product use | |
| 6:30 AM-11:15 PM | | Collection of all used Tobacco Sticks and smoked CC butts | For accountability |
| | | Collection of all tobacco plugs and filters from all used Tobacco Sticks in | For analysis of combustion occurrences and filter analysis |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day 5** | |
| | | dedicated vials | |

Abbreviations: AE = adverse event; BoExp = biomarkers of exposure; CAF = caffeine; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU-brief = Questionnaire of Smoking Urges (brief version); SA = smoking abstinence; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2; T0 = first product use; VAS = visual analog scale.

### 9.2.4 Day of Discharge (Day 6)

Table 15 shows the assessments that will be performed on Day 6, prior to time of Discharge from the study unit:

**Table 15. Time Schedule - Day 6**

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| **Start of procedure** | | **Day of Discharge Day 6** | |
| | | AE/SAE recording; concomitant medication | All day until time of discharge |
| | √ | Nicotine, cotinine in plasma | 20 hours and 24 hours blood sampling after T0 of Day 5 for THS 2.2 and CC arms. Each sample has a time window of +/- 5 minutes<br>For SA arm: 08:00 AM-10:00 AM |
| 06:29 AM+/- 30 min | | Analysis sample to be taken after final portion of urine has been added to Day 5 sampling bottle | BoExp, creatinine, and Ames mutagenicity in 24-hour urine<br>Risk markers: 8-epi-PGF2α and 11-DTX-B2<br>Bio-banking for BoExp/ risk markers in 24-hour urine (if additional consent is obtained) |
| | | Assessment of cough (VAS) | To be done prior to smoking but not later than 10:00 AM |
| | | MNWS questionnaire | To be done prior to smoking but not later than 10:00 AM |
| | √ | CYP2A6 activity in plasma | To be done prior to smoking |
| | | Spirometry without short-acting bronchodilator | To be done prior to smoking |
| | √ | Clinical laboratory parameters (hematology, clinical chemistry) | To be done after at least 8 hours of fasting |
| | √ | Bio-banking for BoExp/ risk markers in serum/plasma (if consent is obtained) | To be done after at least 8 hours of fasting |
| | √ | Bio-banking for transcriptomics (if consent is obtained) | To be done after at least 8 hours of fasting |
| Before discharge | | Urine safety analysis | |
| Before discharge | | Urine pregnancy test (all females) | |
| before 10:00 AM | | Breakfast | |

| Time | Blood sample | Procedures | Additional information |
|---|---|---|---|
| Before discharge | | CO breath test | |
| Before discharge | | Physical examination, and weight and calculated BMI | |
| Before discharge | | Vital signs (blood pressure, pulse rate, respiratory rate) | At least 5 minutes in supine position prior to measurement |
| Before discharge | | ECG | At least 10 minutes in supine position prior to recording |
| Before discharge | | Advice on risk of smoking and debriefing | |
| | | Discharge | |

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; BMI = body mass index; BoExp = biomarkers of exposure; CO = carbon monoxide; CYP2A6 = Cytochrome P450 2A6 ECG = electrocardiogram; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); SA = smoking abstinence; SAE = serious adverse event; VAS = visual analog scale.

## 9.3 Safety Follow-up Period

After subjects have completed the assessments at Day 6 (or if they are prematurely withdrawn from the study), they will enter a 7-day safety follow-up period after the time of Discharge.

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

Any AEs or SAEs that are ongoing at the end of the 7-day safety follow-up period will be handled as described in Section 8.

## 9.4 Early Termination Procedures

The assessments of the Day of Discharge will be performed as early termination procedures (see Section 9.2.4).

# 10 CONTROL AND QUALITY ASSURANCE

## 10.1 Monitoring

A Clinical Research Associate (CRA; "Monitor") not involved with the study site will be responsible for the monitoring of the study. Monitoring will be performed according to the study CROs SOP and as per the agreed monitoring plan with the Sponsor.

The Investigator or designee 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 or designee shall access medical records for the Monitor in order that entries in the eCRFs may be verified. The Investigator or designee, 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.

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

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

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

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

## 10.2 Training of Staff

A formal meeting (Investigator's meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training including a formal GCP 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 Investigator or designee will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and

that any new information relevant to the performance of this study is forwarded to the staff involved in a timely manner. The Investigator or designee will maintain a record of all individuals involved in the study.

## 10.3 Audits and Inspections

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

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

The Investigator or designee and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the Investigator or designee 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 (DMP) and documents specified therein.

## 11.1 Data Capture

### 11.1.1 Case Report Forms and Study Records

With the exception of the subject reported outcome data, all results from the clinical assessments will be recorded in the Source Documents by the Investigator or their authorized designee 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 ePRO device or a paper copy. Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol in the Source Documents and then transferring the data into the eCRF according to the eCRF Completion Guidelines.

The Investigator or designee 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 or designee 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 or designee for resolution. An eCRF will be generated for all subjects that sign the informed consent.

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

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

### 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 Data Structure Specifications.

# 12 PLANNED STATISTICAL METHODS

## 12.1 General Considerations

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

### 12.1.1 Stratification Criteria

For 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 Screening.

### 12.1.2 Definitions for Statistical Data Analysis

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

### 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 [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 (CV) will be presented in addition to the mean and SD.

### 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 approach.

For questionnaire data, total scores and domain or subscale scores may use a certain degree of imputation by averaging across individual item scores.

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.

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 (CIs) will be two-sided 95% CIs.

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.

Full details of this approach 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 4 selected primary BoExps in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

Table 16 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 and the two control arms based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study that investigated exposure to selected smoke constituents in smokers switching from CC to smoking article cigarettes for 5 days, the YVD-CS01-EU study (ClinicalTrials.gov: ID: NCT00812279) sponsored by PMI.

**Table 16. Coefficients of Variation (YVD-CS01-EU study)**

| | THS 2.2 /CC MR (CV) | THS 2.2 /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 17 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 and the CC control arm 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, but otherwise 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.

**Table 17. Coefficients of Variation (ZRHX-EX-01 study)**

| | THS 2.2 /CC 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, the power to demonstrate a reduction was computed. Table 18 describes the expected power to demonstrate a reduction on 4 primary BoExps in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC, using one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and ZRHX-EX-01 and 160 smokers (80 in THS 2.2, 40 in CC, and 40 in the SA arm).

**Table 18. Expected power (YVD-CS01-EU and ZRHX-EX-01 studies assumptions)**

| | Reduction | | | | | |
|---|---|---|---|---|---|---|
| Assumptions | 50% | 51% | 52% | 53% | 54% | 55% |
| YVD-CS01-EU | 96% | 91% | 85% | 75% | 63% | 48% |
| ZRHX-EX-01 | >99% | >99% | 96% | 81% | 48% | 16% |

A total of 160 smokers (80 in THS 2.2, 40 in CC, and 40 in the SA arm) will be randomized to demonstrate to demonstrate a reduction of at least 50% on 4 primary BoExps in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC, using one-sided test with 2.5% type I error probability.

**Power considerations related to secondary endpoints of biological changes:**

The sample size is sufficient to obtain 95% CIs for the ratio between (geometrical) mean levels of primary BoExps in THS 2.2 and SA see Section 12.2 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 and CC in CYP1A2 activity, as measured by the CAF 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 and CC 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 is assumed to be about 90% of the effect of smoking cessation reported in the paper by Saareks et al, 2001.

## 12.3 Analysis Population

The main population for non-safety analysis will be the full analysis set (FAS) population. The per-protocol (PP) population will be used only for the analysis of the primary endpoint to examine the robustness of the primary analyses.

Safety will be analyzed using the safety population.

### 12.3.1 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 or CC, and have at least one valid non-safety assessment (THS 2.2, CC, SA arms).

### 12.3.2 Per Protocol Population

The PP population is a subset of FAS and includes all randomized subjects who fulfill key compliance criteria of the protocol, and have no major protocol deviation (to be further described in the SAP).

### 12.3.3 Safety Population

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

## 12.4 Primary Analysis

### 12.4.1 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.

See section 3.4.1.

Evaluation Criterion: The study will be considered successful if the study demonstrates a 50% reduction or more for all four primary BoExp in the THS 2.2 arm compared to the CC arm (as measured on Day 5), using a one-sided test with 2.5% type I error probability.

### 12.4.2 Baseline Comparability

Not applicable.

### 12.4.3 Descriptive Analysis

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

Should more than 20% of the subjects be excluded from the FAS population, the above descriptive analysis will be repeated on the PP population.

### 12.4.4 Confirmatory Analysis

The hypothesis to be tested for each of the primary and secondary biomarkers of exposure is that the geometric mean level on Day 5 of the biomarker for THS 2.2 is lower relative to CC.

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 geometric means of the biomarker levels on Day 5 for THS 2.2 and CC respectively.

The transformed 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. Estimates of differences between groups will be back-transformed to provide relative effects.

Assumptions of the analysis of variance 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 FAS, would the above confirmatory analysis will be repeated on the PP population.

## 12.5 Secondary Analysis

### 12.5.1 Secondary Endpoint Analysis Variables

See section 3.4.2

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

### 12.5.2 Baseline Comparability

Not applicable.

### 12.5.3 Descriptive Analysis

In general, secondary endpoints will be summarized as described in Section 12.1.3 on the FAS.

### 12.5.4 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 event data will serve as the primary assessment of safety. Other safety variables monitored in this study include: respiratory symptoms (cough assessment VAS and Likert scales); vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; clinical chemistry, hematology, 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 and preferred term. Summaries will also be presented for AEs leading to withdrawal, AEs leading to death, AEs by relatedness to product exposure, AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

The number and percentage of subjects with clinical findings will be tabulated by sequence for laboratory parameters. Shift tables showing change from baseline of clinical findings will be provided for: ECGs, physical examinations, and laboratory parameters (both shifts in normal ranges and toxicity grades). Descriptive statistics will be summarized by visit and change from baseline for laboratory parameters, ECG, respiratory symptoms, and vital signs.

## 12.6 Exploratory Analysis

### 12.6.1 Exploratory Endpoint Analysis Variables

See section 3.4.3.

### 12.6.2 Baseline Comparability

Not applicable.

### 12.6.3 Descriptive Analysis

In general, exploratory endpoints will be summarized as described in Section 12.1.3 on the FAS.

## 12.7 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be reported for safety population. 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.

## 12.8 Interim Analysis

There are no planned interim analyses.

# 13 ADMINISTRATIVE CONSIDERATIONS

## 13.1 Investigators and Study Administrative Structure

### 13.1.1 Investigator

| | |
|---|---|
| **Principal Investigator:** | **Katarzyna Jarus-Dziedzic, MD, PhD (PI)**<br>**BioVirtus Research Site Sp. z o.o.**<br>[redacted] |

### 13.1.2 Sponsor

| | |
|---|---|
| **Sponsor:** | Philip Morris Products S.A.,<br>Quai Jean Renaud 5<br>2000 Neuchâtel<br>Switzerland<br>Phone: + 41 (58) 242 2111<br>Fax: + 41 (58) 242 2811 |
| [redacted], PhD<br>Manager Clinical Science | Phone: +41[redacted]<br>Mobile: +41 [redacted]<br>E-mail:[redacted]@pmi.com |
| [redacted], MEng, MSc<br>Biostatistician | Phone: +41[redacted]<br>Mobile: +41[redacted]<br>E-mail:[redacted]@pmi.com |
| [redacted], MD<br>Medical Safety Officer | Phone: +41 [redacted]<br>Mobile: +41[redacted]<br>Email:[redacted]@pmi.com |
| [redacted], PhD<br>Clinical Study Manager | Phone: +41 [redacted]<br>Mobile: +41[redacted]<br>E-mail:[redacted]@pmi.com |
| [redacted] | Phone: +41[redacted] |

| | |
|---|---|
| Medical Writer | Mobile: +41[redacted]<br>E-mail:[redacted]@pmi.com |

### 13.1.3 Other Responsibilities

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 confidentiality of data for 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, social security number, medical chart number, etc). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

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

## 13.3 Access to Source Documentation

Subjects will be informed that, during the course of the clinical study, the Sponsor, any authorized representatives of the Sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and ensure that all personal information

made available for inspection is handled in the strictest confidence and in accordance with national and local data protection and privacy legislation.

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

## 13.4 Record Retention

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

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in Section 8 of the ICH Tripartite Guideline for GCP (ICH Guideline for Good Clinical Practice E6 (R1), July 1996).

Essential documents must be retained by the Investigator or designee 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 information sheet.
- Subject identification code list, Screening Log, and Enrolment Log (if applicable).
- Record of all communications between the Investigator or designee and the IEC, composition of the IEC.
- Record of all communications/contact between the Investigator or designee, Sponsor, and its authorized representatives.
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curricula vitae, and their signatures.

- Investigator Logs.
- eCRFs, study specific questionnaires (and associated data/scoring), and 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, and dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

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

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

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

The Investigator or designee must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If an Investigator or designee 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 will ensure that a CSR for this study is prepared regardless of whether the study is completed or prematurely terminated.

The CSR will be written based on standards of the ICH Guideline for the Structure and Content of Clinical Study Reports. In certain circumstances, an abbreviated CSR may be

acceptable. Submission of the CSR to the IEC will be complied with as requested by local requirements.

## 13.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor. In addition, the Investigators must 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.

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

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# Appendix 1 Schedule of Events

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

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-30 to -3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **6-13** |
| Informed consent | ● | | | | | | | | | | |
| Admission/Discharge | | ● | | | | | | | | ● | |
| Advice on the risk of smoking and debriefing | ● | ● | | | | | | | | ● | |
| Support for SA arm | | | | | ● | ● | ● | ● | ● | | |
| Inclusion/exclusion criteria | ● | ● | | | | | | | | | |
| Enrolment | | ● | | | | | | | | | |
| Randomization | | | | ● | | | | | | | |
| Demographics, medical history, concomitant diseases | ● | | | | | | | | | | |
| Vital signs [a] | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | |
| Physical examination [b] | ● | ● | | | | | | | | ● | |
| Spirometry [c] | ● | | | ● | | | | | | ● | |
| Prior/concomitant medication | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| B/U: Hematology, clinical chemistry, urine analysis | ● | | | ● | | | | | | ● | |
| Electrocardiogram | ● | | | | | | | | | ● | |
| Chest X-ray [d] | ● | | | | | | | | | | |
| B: HIV, hepatitis B and C | ● | | | | | | | | | | |
| U: Urine drug screen, urine cotinine screening test | ● | ● | | | | | | | | | |
| U: Pregnancy test | ● | ● | | | | | | | | ● | |
| Alcohol breath test | ● | ● | | | | | | | | | |
| FTND | ● | | | | | | | | | | |
| Smoking history | ● | ● | | | | | | | | | |

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-30 to -3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **6-13** |
| Willingness to quit smoking [e] | ● | ● | | | | | | | | | |
| Identification of cigarette brand | ● | ● | | | | | | | | | |
| THS 2.2 demonstration | ● | | | | | | | | | | |
| THS 2.2 product test [f] | | ● | | | | | | | | | |
| CO breath test [g] | | ● | ● (x4) | ● (x4) | ● (x4) | ● (x4) | ● (x4) | ● (x4) | ● (x4) | ● | |
| B: BoExp in blood: COHb [h] | | | ● | ● | ● | ● | ● | ● | ● (x4) | | |
| B: Biomarker of exposure in plasma: nicotine, cotinine [i] | | | | ● | ● | ● | ● | ● | ● | ● | |
| B: CYP1A2 activity | | | | ● | | | | | ● | | |
| B: CYP2A6 activity | | | | ● | | | | | | ● | |
| QSU-brief questionnaire [j] | | | ● | ● | ● | ● | ● | ● | ● | | |
| MNWS (revised version) [k] | | | | ● | ● | ● | ● | ● | ● | ● | |
| MCEQ (modified version; THS 2.2 and CC arms) [l] | | | ● | ● | ● | ● | ● | ● | ● | | |
| HST (THS 2.2 and CC arms) [m] | | | | ● | ● | | | ● | | | |
| HST questionnaire (THS 2.2 and CC arms) [m] | | | | ● | | | | ● | | | |
| Assessment of cough | | | | ● | ● | ● | ● | ● | ● | ● | |
| AE/SAE recording | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Collection of tobacco plugs and filters from all used Tobacco sticks for analysis of combustion occurrences and filter analysis and for accountability | | | | | ● | ● | ● | ● | ● | | |
| Collection of used CC butts for accountability | | | ● | ● | ● | ● | ● | ● | ● | | |
| B: Bio-banking for biomarkers of exposure and risk markers [n] | | | | ● | | | | | | ● | |

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-30 to -3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **6-13** |
| B: Bio-banking for transcriptomics[n] | | | | ● | | | | | | ● | |

Abbreviations: AE = adverse event; B = blood; BoExp = biomarker(s) of exposure; BMI = body mass index; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP1A2 = cytochrome P450 1A2; CYP2A6 = cytochrome P450 2A6; FTND = Fagerström Test for Nicotine Dependence; HIV = human immunodeficiency virus; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale (revised version); QSU -brief= Questionnaire of Smoking Urges (brief version); SA = smoking abstinence; SAE = serious adverse event; T0 = first product use; THS 2.2 = Tobacco Heating System 2.2; U = urine.

a: Systolic and diastolic blood pressure, pulse rate, and respiratory rate

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

c: Spirometry has to be done prior to smoking on Day 0 and Day 6. At screening, spirometry needs to be done prior at least 1 hour after smoking.

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

e: Subjects will be asked if they plan to quit smoking within the next 3 months (at Screening only) and, in order to satisfy the protocol inclusion criteria, if they are ready to abstain from smoking for at least 5 days (at Screening and Day -2).

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

g: On Days -1 to Day 5, the CO breath test will be conducted 4 times per day. For subject in the THS 2.2 and CC arms, the first test should be conducted prior to the first product use. The other 3 tests should be conducted as described in section 9.

On Days 1 to Day 5, the CO breath test will be conducted 4 times per day. for subjects in the SA arm, the first CO breath test will be done 08:00 AM-10:00 AM. The other three tests will be conducted as described in section 9.

On Day -2 and Day 6, the CO breath tests will be conducted once.

h: COHb; Assessments should be done in conjunction with CO breath tests, where applicable. Day -1 to Day 4: one blood sample in the evening as described in section 9.

Day 5: four blood samples will be collected 4 times per day. one blood sample prior to the first product use (for subjects in the THS 2.2 and CC arms) and 08:00-10:00 AM for subjects in the SA arm, and the three remaining samples as described in section 9.

i: Nicotine/cotinine; Day 0 to Day 4 (all study arms): one blood sample 08:00 PM:10:00 PM.

Day 5 and Day 6 (THS 2.2 and CC arms): one sample within 15 minutes prior to the T0; eight blood samples after 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 08:00 PM-10:00 PM. On Day 6, one blood sample to be drawn 08:00 AM-10:00 AM.

j: QSU-brief: Daily, from Day -1 to Day 5.

k: MNWS daily from Day 0 to Day 6.

l: MCEQ: Day -1 to Day 5 on a daily basis.

m: On Day 0, HST and HST questionnaire will be done in all subjects smoking CC compatible with the HST SODIM® device. On Day 1 and Day 4, HST and HST questionnaire will be done in all subjects in the THS 2.2 and CC arms. Smoking topography with the HST SODIM® device will not be done in subjects smoking CC that are incompatible with the HST SODIM® device (e.g. slim CC). No HST assessments will be done in subjects in the SA arm.

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

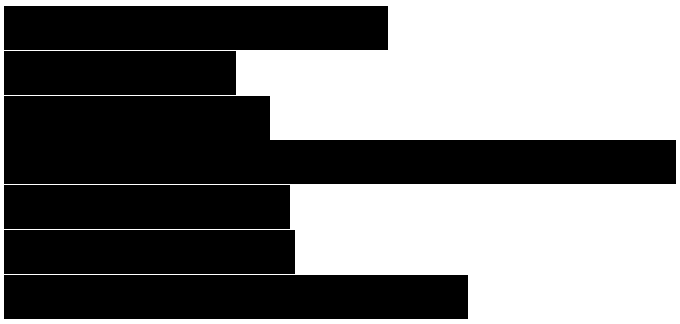
**Table A2 Schedule for 24-hour Urine Collection Assessments**

| | Baseline period | | Confinement Exposure Period | | | | |
|---|---|---|---|---|---|---|---|
| **24 hour urine samples** | **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** |
| BoExp in urine | ● | ● | ● | ● | ● | ● | ● |
| Creatinine | ● | ● | ● | ● | ● | ● | ● |
| Ames mutagenicity test, 11-DTX-B2 and 8-epi-PGF2α | | ● | | | | | ● |
| Bio-banking | | ● | | | | | ● |

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; BoExp = biomarker(s) of exposure.

## Appendix 2 Participating Laboratories

1) Clinical safety laboratory services will be provided by:



2) The following laboratory will analyze urine, blood and plasma samples for the BoExp and risk markers:

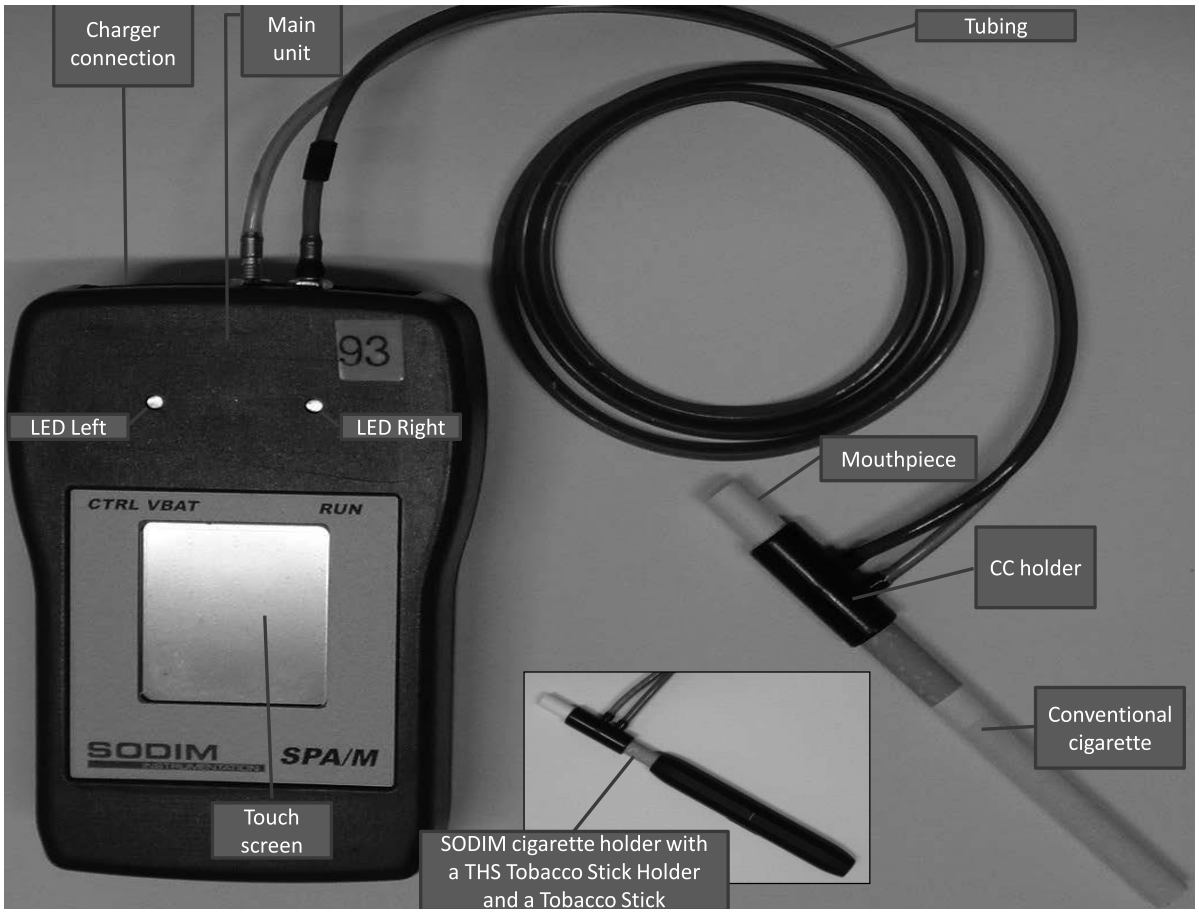
3) The urine samples for the BoExp, 4_ABP, 2-NA, total 1-OHP and o-tol will be analysed at the following laboratory:

## Appendix 3 Investigational Product and Instructions for Use

The product user guide will be provided as a separate document. The site should insert the manual here in the protocol binder.

## Appendix 4 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 staff before study start.



# Appendix 5 Abnormal Laboratory Values

## CTCAE 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)<br>(mmol/l) | <LLN - 55;<br><LLN - 3.0 | <55 - 40;<br><3.0 - 2.2 | <40 - 30;<br><2.2 - 1.7 |
| Glucose – Hyperglycemia: ** (1)<br>Fasting (mg/dl)<br>(mmol/l)<br>Non-fasting (mg/dl)<br>(mmol/l) | <br>>ULN-160;<br>>ULN-8.9<br>-<br>- | <br>>160-250;<br>>8.9-13.9<br>-<br>- | <br>-<br>-<br>>250-500;<br>>13.9-27.8;<br>hospitalization indicated |
| Blood Urea Nitrogen (BUN) (mg/dl) (2) | 23 - 26 | 27 - 31 | > 31 |
| Creatinine increased** (1) | >1 - 1.5 x baseline;<br>>ULN - 1.5 x ULN | >1.5 - 3.0 x baseline;<br>>1.5 - 3.0 x ULN | >3.0 x baseline;<br>>3.0 - 6.0 x ULN |
| Albumin - Hypoalbuminemia** (1) (g/dl)<br>(g/l) | <LLN - 3;<br><LLN - 30 | <3 - 2;<br><30 - 20 | <2;<br><20 |
| Total Protein - Hypoproteinemia (2)<br>(g/dl) | <br>5.5 - 6.0 | <br>5.0 - 5.4 | <br>< 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)<br>(mg/dl)<br>(mmol/l) | <br>>ULN - 300;<br>>ULN - 7.75 | <br>>300-400;<br>>7.75-10.34 | <br>>400-500;<br>>10.34-12.92 |
| Triglycerides - Hypertriglyceridemia (1)<br>(mg/dl)<br>(mmol/l) | <br>150 - 300;<br>1.71 - 3.42 | <br>>300 - 500;<br>>3.42 - 5.70 | <br>>500 - 1000;<br>>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.

## CTCAE ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

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

Abbreviations: LLN = lower limit of the normal range; ULN = upper limit of the normal range; WBC = white blood cell.

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

(2) Common Terminology Criteria for Adverse Event and Common Toxicity Criteria (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.

## CTCAE 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 Event and Common Toxicity Criteria (CTCAE) version 4.03.

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

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

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