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## STATISTICAL ANALYSIS PLAN

## A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting

Study Product: Tobacco Heating System 2.2 Menthol

Sponsor Reference No.: ZRHM-REXA-08-US
CDARO No.: 1001000-8278008

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### Confidentiality Statement

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# 1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

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

███████ approval:

_____, MS          _____
**Statistician**                              **Date**

**Sponsor approval:**

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# 3    INTRODUCTION

This SAP has been developed to supplement the statistical analysis described in the clinical study protocol (final version 5.0 dated 14 April 2014).

This SAP describes the methodology and considerations of the planned analyses and a list of all the TFLs for this study. A detailed description of the planned TFLs will be provided in a separate TFLs shell document. Any changes to the TFL shells numbering or to the title of the TFLs will not require an amendment to this SAP.

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

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

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (**ICH Guideline E9 1998**)
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (**ICH Guideline E3 1995**)
- Electronic case report forms (eCRF) final version 1.0 (dated 28 January 2014).
- Biostatistical Addendum – Subject Randomization List version 1.0 (06 March 2013).

## 3.1    Revision History

| Version | Date of Revision | Revision |
| --- | --- | --- |
| 3.0 | 29 May 2015 | o Amended table titles and numbers after review by client and to ensure consistency between titles in the SAP and TFL shells,<br>o Deleted tables no longer required after review by client<br>o Removed percentage change end points from the concordance analysis between the urine biomarkers from the 24 hour sample and the 4 hour urine fraction.<br>o Removed 4-hour fraction data expressed as quantity excreted when summarizing urinary BoExp, risk markers, and NEQ; and when comparing concordance of urinary BoExp, risk markers, and NEQ with 24-hour urine collection results.<br>o Removed 4-hour fraction data from analyses of subjects quitting smoking<br>o Removed ISO tar yields and ISO nicotine level from Section 12.3.1<br>o Sections 12.6.3.5 and 12.6.3.6 have been removed as no longer an objective of the study |
| 2.0 | 12 January 2015 | o Deleted abbreviations from Section 4 that no longer apply to the study |

| Version | Date of Revision | Revision |
|---|---|---|
| | | o Updated objectives in Section 5.3 to reflect all oxysterols listed in the protocol. |
| | | o Updated Inclusion/Exclusion criteria in Section 6.2 to reflect the text in the protocol. |
| | | o Updated Blinding in Section 6.3.2 to reflect that the study scientist is unblinded for the data review meeting. |
| | | o Abstinence category (100% abstinence) biochemically verified with CO breath test in Section 6.3.3.2. Removed the reference to CEMA study because no longer found to be relevant. |
| | | o Re-organized Section 7.1 in order to concisely describe methods for both urinary BoExp and risk markers. Methods for LLOQ/ULOQ data handling moved in Section 12.1.5. |
| | | o Specified units for Puff number and frequency, and fixed typo in the Average inter puff interval calculation in Section 7.1 |
| | | o Included changes from the protocols for Blinding in Section 9. |
| | | o Reworded Analysis population Section 10 in order to clarify the definition of per protocol set which is separately defined on each analysis period (as defined in Section 11.1.1). Clarified that safety populations may be different pre and post randomization, and that product use categories will be defined over the whole ambulatory period. |
| | | o In Section 11.1.1, clarified that: <br>    o Product compliance will be defined using the product distribution log in confinement and the eDiary in Ambulatory <br>    o Non compliance is defined for each period <br>    o The violation of inclusion criteria 1,2,3, and 4 and exclusion criteria 2, and 21 will be interpreted as impacting evaluability, other violations will be interpreted during the data review |
| | | o Included in section 11.1.2 procedural violation category and updated concomitant medication category so to include drugs known to affect 11-DTX-B2 and CYP1A2. |
| | | o Clarified in Section 12.1 that stratified presentation will be performed at period 1 and 4 for the PP set on Baseline characteristics, endpoints for primary objective, and product use. |
| | | o Summarized in Section 12.1.3 the general methods for descriptive statistics of biomarkers and safety data and removed any related text from each endpoint specific section (Section 12.6.1, 12.6.2, 12.6.2.5, and 12.6.4). |
| | | o Listed in Section 12.1.3 the TFL labels used for randomized product use and for stratification factors |
| | | o Clarified the definition of Baseline in Section12.1.4, |

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| | | using 10:00am on Day 1 as a reference for SA arm<br>○ Clarified in Section 12.1.5 the imputation rules for BoExp, CYP1A2, CYP2A6 and risk markers using the last observation carried forward; the missing data handling derivation rules for daily product use for safety and non-safety analysis and summaries . In this section, it was also clarified how the missing dates will be imputed for safety interpretation (for adverse events, diseases, and medications) and for product use calculation<br>○ Clarified the definitions of Enrolled subjects and Visit completion status for study subjects in Section 12.2.<br>○ Reorganized list of tables, listing and figures in Sections 12.2 to 13.5<br>○ in Section 12.3.1: the tabulation of mCC brands was limited to brands used by at least 4 subjects; fixed a typo for the definition of the ISO nicotine levels categories. Removed readiness to accept interruption and risk of smoking because not included in the data base.<br>○ Socio-Economic Status questionnaire data (Section 12.3.2) summarized together with the Baseline characteristics and clarified questions to be asked.<br>○ In Section 12.3.3, clarified that concomitant disease is defined as any condition that was ongoing at Screening. AEs related text moved into Section 12.6.4.2<br>○ In Section 12.3.4, Debriefing of risk of smoking are removed as not included in the SDTM data base. Product preference and Willingness to use the product will be summarized together with Baseline characteristics.<br>○ Clarified that the level of CO will serve as compliance tool starting from Day 2, because of possible carry over effect (in Section 12.4)<br>○ In Section 12.5, text was adapted to the updated definition of analysis periods (1 to 4). Clarified that summaries for the FAS will be produced only if this set differs from the Safety population by more than 10%<br>○ In Section 12.6.1.1:<br>  ○ Title was changed so to reflect that the analyzed endpoints were serving for the evaluation of the primary objectives.<br>  ○ Clarified the value to be used in the analysis for repeated measurement on analysis day (e.g. COHb at Day 5)<br>  ○ A proc GLM approach will be used for the analysis of THS 2.2 and mCC data. Results will be graphed in a Forest plot<br>○ In Section 12.6.1.3, a sensitivity analysis was added for the analysis of Section 12.6.1.1 by means of a mixed model approach without LOCF missing |

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|         |                  | imputation. Clarified that the sensitivity analysis on the compliant population will be produced also for the comparison between THS 2.2 Menthol and SA.<br>○ In Section 12.6.2 and 12.6.2.5:<br>　○ Added summaries for the endpoints of the primary analysis<br>　○ Clarified that the p-value will only be produced at Day 90 conditionally on the statistical significance at Day 5<br>　○ Clarified that the CO breath test will be analyzed Iin the regular scale<br>　○ Text and list of TFL adjusted according to the general rules for summaries of BoExp<br>　○ Summaries of Nicotine and cotinine concentration not produced as a change from baseline and data will be analyzed on the log space. The mixed model code was removed to analyze results using ANCOVA by timepoint for consistency with other analyses.<br>　○ Clarified that the ratio will be estimated for the analysis of nicotine and cotinine $C_{peak}$ and $C_{avg}$ on Day 5. The median difference will be tabulated for the $t_{peak}$ on Day 5 .<br>　○ CYP1A2 and CYP2A6 activity will be analyzed in the log space and the THS 2.2 Menthol:mCC ratio will be presented.<br>　○ Percent change from Baseline will be summarized and listed for the QSU-brief. Data will be analyzed using the same model adopted for the analysis pf nicotine and cotinine over study days, amended as appropriate to obtain the required comparison. Only Total score data will be plotted.<br>　○ Summaries and listing of percent change from Baseline added for mCEQ, MNWS, and Ames mutagenecity. Clarified that for the MNWS the results will be presented for the day prior to the assessment.<br>　○ Section of HST questionnare data moved within the questionnaires Section 7.3.6.<br>　○ Risk markers analyzed for the FAS and PP set. Blood pressure, HbA1c, LDL, HDL, TG, TC, WBC, body weight and waist circumference will be analyzed in the regular scale. 8-epi-PGF2a, 11 DTX-B2, sICAM will be analyzed in the logarithmic scale. Other risk markers will be logarithmically transformed prior to analysis if there is evidence of non-normality by means of Shapiro-Wilks test.<br>○ In Section 12.6.4: |

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|---------|-----------------|----------|
| | | o Clarified that AE and laboratory findings summaries will be produced also for the Full Safety population<br>o Clarified that only product emergent AE will be summarized.<br>o Clarified that Pre and post randomization safety data will be summarized separately.<br>o Clarified that ambulatory AE data will also be reported by product use category defined on the product use over the whole ambulatory period. No other safety data will be summarizd by product use categories, and text was reworded accordingly.<br>o Updated that THS 2.2. Device Events will be classified according to a PMI internal device controlled terminology instead of the C54451/Medical Device codes from FDA.<br>o Clarified that toxicity grading will be summarized for the laboratory findings together with their changes and shift in normality.<br>o Modified any occurrence of "clinical relevance" to "clinical significance".<br>o Clarified that results from the cough questionnaire will be presented for the day prior to the assessment |
| 1.0 | 30 September 2013 | Original SAP sent to the FDA |

# 4     ABBREVIATION OF TERMS AND SPECIAL TERMS

The following abbreviations are used within this SAP.

| | |
|---|---|
| 1-NA | 1-aminonaphthalene |
| 1-OHP | Total 1-hydroxypyrene |
| 2-NA | 2-aminonaphthalene     3-HPMA |
|   3-hydroxypropylmercapturic acid   4-ABP     4-aminobiphenyl | |
| 8-epi-PGF2$a$ | 8-epi-prostaglandin F2$a$ |
| 11-DTX-B2 | 11-dehydro-thromboxane B2    AE/SAE Adverse Event/ Serious Adverse Event |
| ANCOVA | Analysis of Covariance ANOVA |
| Analysis of Variance | |
| ATC | Anatomical Therapeutic and Chemical |
| $AUC_{0\text{-}24\,h}$ | The area under the curve from 0 to 24 h |
| B[a]P | 3-hydroxybenzo(a)pyrene |
| BMI | Body Mass Index |
| BoExp | Biomarkers of exposure |
| CAF | Caffeine |
| $C_{avg}$ | The weighted average concentration for nicotine or cotinine over 24 hours on Day 5 |
| CC | Conventional Cigarettes |
| CEMA | 2-cyanoethylmercapturic acid |
| CI | Confidence Interval |
| CO | Carbon Monoxide |
| COHb | Carboxyhaemoglobin |
| $C_{peak}$ | The peak nicotine and cotinine plasma concentration |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events and Common Toxicity Criteria |
| CV | Coefficient of Variation |
| CYP1A2 | Cytochrome P450 1A2 |

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| | |
|---|---|
| CYP2A6 | Cytochrome P450 2A6 |
| DLCO | Diffusion capacity for lung carbon monoxide |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EOS | End of Study |
| FAS | Full analysis set |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FRV | Forced residual volume |
| FTND | Fagerström Test for Nicotine Dependence |
| FVC | Forced Vital Capacity |
| HbA1c | Hemoglobin A1c |
| HDL | High-density lipoprotein |
| HEMA | 2-hydroxyethyl mercapturic acid |
| HIV | Human Immunodeficiency Virus HMPMA |
| 3-hydroxy-1-methylpropyl-mercapturic   acid | |
| HST | Human Smoking Topography |
| hs-CRP | High-sensitive C-reactive protein |
| IC | Inspiratory capacity |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ISO | International Organization for Standardization |
| ITT | Intention-to-treat |
| IXRS | Interactive Voice and Web Response System |
| KCO | Rate constant for lung carbon monoxide |
| LDL | Low density lipoprotein |
| LLOQ | Lower Limit of Quantification |
| LS | Least Squares |
| mCC | Single preferred brand of menthol CC |
| MCEQ | Modified Cigarette Evaluation Questionnaire |
| MedDRA | Medical Dictionary for Regulatory Activities |

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| | |
|---|---|
| MHBMA | Monohydroxybutenyl mercapturic acid |
| MNWS | Minnesota Nicotine Withdrawal Scale |
| MR | Mean ratio |
| NEQ | Nicotine equivalents |
| NNAL | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol |
| NNN | Total N-nitrosonornicotine |
| NRT | Nicotine replacement therapy |
| NSAIDS | nonsteroidal anti-inflammatory drugs |
| o-tol | o-toluidine |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PP | Per protocol |
| PT | Preferred Term |
| PX | Paraxanthine |
| QC | Quality Control |
| QSU-brief | Urge-to-Smoke Questionnaire of Smoking Urges Brief |
| QTcB | QT Interval Corrected using Bazett's Formula |
| QTcF | QT Interval Corrected using Fridericia's Formula |
| SA | Smoking abstinence |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| S-BMA | S-benzylmercapturic acid |
| s-ICAM-1 | Soluble inter-cellular adhesion molecule 1 |
| S-PMA | S-phenylmercapturic acid |
| TC | Total cholesterol |
| TFL | Tables, Figures, and Listings |
| TG | Triglycerides |
| THS | Tobacco Heating System |
| TLC | Total lung capacity |

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| $t_{peak}$ | Time to peak concentration |
| ULOQ | Upper Limit of Quantification |
| VAS | Visual Analogue Scale |
| VC | Vital capacity |
| WBC | White blood cell |
| WHO | World Health Organisation |
| YG1024+S9 | Ames Mutagenicity test |

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The following special terms are used in this SAP:

| | |
|---|---|
| Baseline period | 06:30 AM at Day -1 until 06:29 AM of Day 1. |
| Menthol conventional cigarette (mCC) | The term 'menthol conventional cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products. |
| mCC incompatible with Human Smoking Topography (HST) device | All mCCs that are incompatible with the HST device (e.g., slim mCC). |
| Day of Discharge from confinement | Day 6: when the subject is released from the site (confinement period) prior to entering into the ambulatory period. |
| Day of discharge from ambulatory period | Day 91: when the subject is released from the site on Day 91 and enters the 28-day safety follow-up period. |
| Enrollment | On Day -2 eligible subjects are enrolled after all inclusion and exclusion criteria have been satisfactorily met and the subject is willing and ready to use THS 2.2 Menthol (the test of THS 2.2 Menthol is the last assessments prior to enrollment). |
| Exposure period | 06:30 AM of Day 1 until time of discharge on Day 91 |
| Randomization | Assignment of the subject randomization number in the Interactive Web and Voice Response System (IXRS). This can be done any time on Day 0, however, subjects are not to be informed of their randomization group prior to Day 1. |
| Run-in period | Time of admission to the site until 06:29 AM of Day -1 |
| Safety follow-up | After the time of Discharge on the Day 90 Visit, a 28-day safety follow-up will be done for the recording of spontaneously reported new adverse events / serious adverse events (AEs/SAEs) and the active follow-up of ongoing AEs/SAEs by the study site. |
| Screening failure | Subjects who are not enrolled will be considered a screening failure and will be replaced by other subjects. |
| Tobacco Heating System 2.2 Menthol (with Menthol Tobacco Sticks) (THS 2.2 Menthol) | THS 2.2 Menthol comprises the following components: Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable. |

# 5 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Primary Objective and Endpoints

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

   Endpoints:
   - Monohydroxybutenyl mercapturic acid (MHBMA) 24-hour urine concentration adjusted for creatinine on Day 5.
   - 3-hydroxypropylmercapturic acid (3-HPMA) 24-hour urine concentration adjusted for creatinine on Day 5.
   - S-phenylmercapturic acid (S-PMA) 24-hour urine concentration adjusted for creatinine on Day 5.
   - Carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

2. To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoint:
   - Total NNAL 24-hour urine concentration adjusted for creatinine on Day 90 Visit.

## 5.2 Secondary Objectives and Endpoints

1. To evaluate self-reported nicotine/tobacco product use including dual-use in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).

   Endpoint:
   - Number of mCC or Menthol Tobacco Sticks used daily as reported on the usage log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.

2. To determine the reduction of secondary BoExp in a confinement and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints:
   - Quantity Excreted in urine over 24 hours for MHBMA, S-PMA and 3-HPMA.
   - Carbon monoxide (CO) (expressed as ppm) in exhaled breath.

- Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine on Day 5 and on Day 90 Visit:
  - Total 1-hydoxypyrene (1-OHP).
  - Total N-nitrosonornicotine (NNN).
  - 4-aminobiphenyl (4-ABP).
  - 1-aminonaphthalene (1-NA).
  - 2-aminonaphthalene (2-NA).
  - O-toluidine (o-tol).
  - 2-cyanoethylmercapturic acid (CEMA).
  - 2-hydroxyethyl mercapturic acid (HEMA).
  - 3-hydroxybenzo(a)pyrene (B[a]P).
  - 3-hydroxy-1-methylpropyl-mercapturic acid (HMPMA).
  - S-benzylmercapturic acid (S-BMA).

3. To describe the levels of primary and secondary BoExp over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and SA.

Endpoints (on Days 1 to 5, Day 30 Visit, Day 60 Visit and Day 90 Visit):
- CO (expressed as ppm) in exhaled breath.
- COHb in blood (expressed as % saturation of Hemoglobin).
- Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine:
  - MHBMA.
  - 3-HPMA.
  - S-PMA.
  - Total NNAL.
  - 1-OHP.
  - Total NNN.
  - 4-ABP.
  - 1-NA.
  - 2-NA.
  - o-tol.
  - CEMA.
  - HEMA.
  - B[a]P.
  - HMPMA.
  - S-BMA.

4. To determine the levels of nicotine over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.

Endpoints:
- Nicotine equivalents (NEQ) (expressed in quantity excreted and concentration adjusted for creatinine) in 24-hour urine from Day 1 to Day 5, Day 30 Visit, Day 60 Visit and Day 90 Visit.
- Nicotine and cotinine in plasma from Day 1 to Day 4, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit.

5. To describe the pharmacokinetic (PK) profiles of nicotine and cotinine in smokers in a confinement setting switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints:
   - Peak (highest concentration value along the day) on Day 5.
   - Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
   - Weighted average concentration over 24 hours on Day 5.

6. To describe the change in Cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and SA.

   Endpoint:
   - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5 and Day 90 Visit.

7. To determine the changes in lung function in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC.

   Endpoint:
   Full lung functions:
   - Diffusion capacity for lung CO (DLCO).
   - Rate constant for lung CO (KCO).
   - Forced expiratory volume in 1 second ($FEV_1$).
   - Forced vital capacity (FVC).
   - Vital capacity (VC) expressed as L.
   - Total lung capacity (TLC).
   - Forced residual volume (FRV).
   - Inspiratory capacity (IC).
   - Mid expiratory flow (25-75)

8. To monitor the safety profiles during the study.

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

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

Endpoints:
- Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
- Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) in serum on Day 90 Visit.
- Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- White blood cell (WBC count), including count of differentials, and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-prostaglandin F2$a$ (8-epi-PGF2$a$) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24 hour urine on Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as quantity excreted and concentration adjusted for creatinine).
- Body weight and waist circumference on Day 90 Visit.

## 5.3 Exploratory Objectives and Endpoints

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

Endpoints:
- Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24 hour urine.
- Subjective effect of smoking: Questionnaire of Smoking Urges (QSU-brief questionnaire); questionnaire Minnesota Nicotine Withdrawal Scale (MNWS)-Revised on Day 5 and Day 90 Visit, and nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire score on Day 90 Visit.
- Cytochrome P450 2A6 (CYP2A6) activity: in plasma on Day 6, and on Day 90 Visit using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.

2.  To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing smoking mCC:

    Endpoints:
    - Product evaluation: The subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ).
    - Smoking puffing behavior: HST questionnaire
    - The following parameters measured per cigarette from the HST device.
      - Total number of puffs.
      - Total puff volume.
      - Average puff volume.
      - Average puff duration.
      - Total puff duration.
      - Average flow.
      - Peak flow.
      - Total inter puff interval.
      - Average inter puff interval.
      - Total smoking duration.
      - Total work.
      - Average work.
      - Average pressure drop.
      - Average peak pressure drop.
      - Smoking intensity.
      - Puffing time index.
      - Puff frequency.

3.  To describe the following parameter over the course of the study in smokers switching from mCC to THS 2.2 Menthol:

    Endpoint:
    - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.

4.  To describe the changes in levels of oxysterols on Day 6 and Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol, and in smokers switching from mCC to SA.

    Endpoints:
    - Plasma concentrations of:
      - 6*a*-hydroxy-5*a*-cholestane.
      - 7*a*-hydroxycholesterol.
      - 5*a*,6*a*-epoxycholestanol.
      - 7-ketocholesterol.
      - 7�hydroxycholesterol.
      - 5�,6�-epoxycholestanol.
      - 24(R)-hydroxycholesterol.
      - 25-hydroxycholesterol.
      - 27-hydroxycholesterol.
      - Total cholesterol (TC).
      - 22(R)-hydroxycholesterol.
      - 4ß-hydroxycholesterol.

5.  To describe the product use over the course of the study according to the product preference of the subject.

    Endpoint:
    - Number of mCC or Menthol Tobacco Sticks smoked daily as reported on the usage log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary by product preference.

6.  To describe the smokers' mental state for the intention to quit smoking at Screening, on Day -2, Day 30 Visit, Day 60 Visit, and Day 90 Visit.

    Endpoints:
    - By the means of the Prochaska 'stage of change' questionnaire.

7.  To describe the changes and reductions in the levels of urinary BoExp and risk markers measured in 4-hour urine fraction on Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and SA.

    Endpoints:
    - Urinary BoExp (expressed as concentration adjusted for creatinine) in 4-hour urine fraction:
      - MHBMA.
      - 3-HPMA.
      - S-PMA.
      - Total NNAL.
      - 1-OHP.
      - Total NNN.
      - 4-ABP.
      - 1-NA.
      - 2-NA.
      - o-tol.
      - CEMA.
      - HEMA.
      - B[a]P.
      - HMPMA.
      - S-BMA.
    - Urinary risk markers (expressed as concentration adjusted for creatinine) in 4-hour urine fraction:
      - 8-epi-PGF2$a$.
      - 11-DTX-B2.

8.  To determine the concordance between the results for BoExp and risk-markers in 24-hour urine and 4-hour urine fraction[1].

    Endpoints:
    - MHBMA, 3-HPMA, S-PMA, total NNAL, total 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ (expressed as concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at baseline and at Day 90 Visit.
    - 8-epi-PGF2$a$ and 11-DTX-B2 (expressed as concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at baseline and at Day 90 Visit.

9.  To monitor the BoExp in subjects quitting smoking according to the time since they quit[2].

    Endpoints:

---

[1] *The reporting of this objective will be the subject of an appendix to the main Clinical Study Report.*
[2] *The reporting of this objective will be subject of an appendix to the main Clinical Study Report.*

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- Carbon monoxide (expressed as ppm) in exhaled breath.
- COHb in blood (expressed as % saturation of hemoglobin)
- Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine collection.
- NEQ (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine collection.
- Selected risk markers (hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, HbA1c, Apo A1, Apo B, sICAM-1, WBC count, platelet count, 8-epi-PGF2$a$, 11-DTX-B2) in respective body matrix when available.

## 5.4     Additional Endpoints

The following additional assessments will be made:
- Serology for human immunodeficiency virus (HIV) 1/2 and Hepatitis B and C
- Urine pregnancy test (females only), urine cotinine test, urine drug screen
- Alcohol breath test
- Socio-Economic Questionnaire
- Question on product preference
- Behavioral risk factor surveillance system questionnaire
- Smoking questionnaire
- Chest X-ray

## 5.5        Study Hypotheses And Evaluation Criteria

### 5.5.1   Hypotheses

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

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

### 5.5.2   Evaluation Criteria

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

# 6 INVESTIGATIONAL PLAN

## 6.1 Study Design

This is a randomized, controlled, open-label, 3-arm parallel group, multi-center study. Randomization is stratified by sex and average daily mCC consumption over the last 4 weeks as reported during the Screening Visit (10 - 19 mCC/day vs. >19 mCC/day). (**Figure 1 Study Flowchart**).

In total, 160 female or male smoking, apparently healthy adult subjects who smoke per day at least 10 mCC for the last 4 weeks will be randomized in this study. All races/ethnicities will be considered eligible for the study. The subjects will be randomized into one of the three study arms in **Table 1 Definition of Study Arms**.

## Table 1 Definition of Study Arms

| Study arm | Number of subjects |
| --- | --- |
| THS 2.2 Menthol | 80 |
| mCC | 40 |
| Smoking abstinence | 40 |

This is an *ad libitum* smoking study. In general, smoking/product use during the confinement period will be allowed between 06:30 AM and 11:00 PM. During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from the time of check-in prior to 08:30 AM to around 11:00 PM on Day 30, Day 60, and Day 90. Smoking/product use before 08:30 AM on Day 30, Day 60 and Day 90 are not restricted. During the second day of the Day 30 and Day 60 Visits, product use will be allowed from 06:30 AM onwards. On the second day of the Day 90 Visit, product use will be allowed after the CYP2A6 activity, MNWS and cough questionnaires and spirometry have been performed until time of discharge.

The Screening Visit will be conducted within 4 weeks prior to Admission to the investigational site (Day -30 to Day -3). Screening procedures do not necessarily have to be conducted on the same day. During the Screening Visit the site staff will demonstrate the use of THS 2.2 Menthol.

Prior to enrollment on Day -2, as the last procedure of the eligibility assessments, subjects will have a product test of the THS 2.2 Menthol (use of up to 3 THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product test will only be done after pregnancy is excluded by a negative urine pregnancy test. Enrollment 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.

Subjects are admitted and enrolled on Day -2 but not randomized until Day 0. From Day-2 to Day 0, all subjects continue smoking their single preferred brand of mCC, and baseline values will be recorded. On Day 0, subjects will be randomized to one of the

3 study arms (**Table 1 Definition of Study Arms**). Subjects will be informed of their product allocation by the study site staff on Day 1 prior to 06:30 AM.

The exposure period (from Day 1 06:30 AM until time of Discharge on Day 91 will include both the exposure in confinement and the exposure in the ambulatory setting.

The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product from 06:30 AM onwards until around 11:00 PM in THS 2.2 Menthol and mCC arms. Subjects allocated to the SA arm will be asked to abstain from smoking. Subjects have been allowed to smoke their normal cigarettes prior to Day 1. Subjects will be provided with psychological support during the period of SA. No medication to support SA will be allowed during the confinement period. Use of any tobacco/nicotine-containing product other than the assigned product/regimen will not be allowed and may, at the discretion of the Investigator, result in the withdrawal of the subject from the study.

On Day 6, the safety procedures will be conducted before discharge of the subject from the clinic. Use of products will be allowed on Day 6 in the THS 2.2 Menthol and mCC arms, but only after the sample for CYP2A6 activity, MNWS and cough questionnaires and spirometry have been performed.

At the end of the confinement period (Discharge from the site on Day 6), subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 86 days. Subjects will be allowed to use nicotine replacement therapy (NRT) if considered necessary by the Investigator or requested by the subject.

Subjects will be required to make three visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) during the ambulatory period. Each visit will cover 2 consecutive days on site. For all Visits the subject will check-in in the morning prior to 08:30 AM on the first day and will check-out on the second day.

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

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

After the time of Discharge on the second day of the Day 90 Visit, subjects will enter a 28-day safety follow-up period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found. The end of the study (EOS) is defined as the time of Discharge plus 28-day follow-up.

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**Figure 1    Study Flowchart**



Abbreviations: mCC = Menthol conventional cigarette(s); THS = Tobacco Heating System; Figure not to scale.
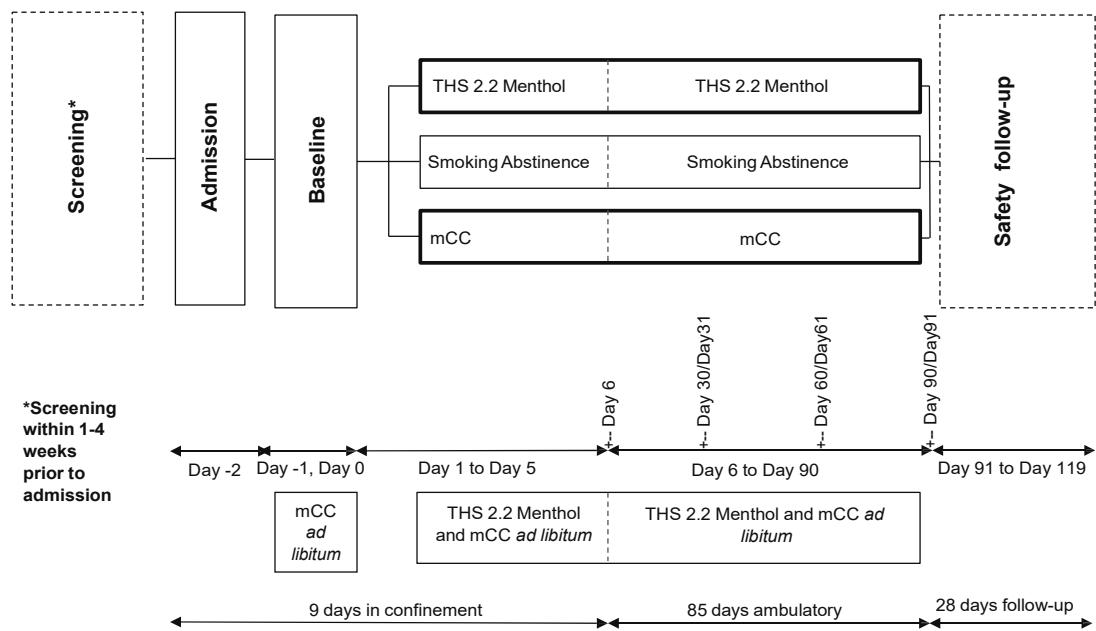
## 6.1.1   Timing of Confinement Period

The 9 day confinement period consists of:

- The Admission Day (Day -2).
- The run-in period is from admission on Day -2 until 06:29 AM of Day -1.
- The baseline period is from Day -1, 06:30 AM until Day 1, 06:29 AM.
- The exposure period in the confinement setting  is from Day 1 06:30 AM until Day the time of Discharge on Day 6 (start of the ambulatory setting).

The exposure period in the ambulatory setting is from the time of discharge on Day 6 to the time of Discharge on the second day of the Day 90 Visit.

## 6.2       Selection of Study Population

### 6.2.1   Inclusion Criteria

The following inclusion criteria will be applicable for this study:

1.   Subject has signed the informed consent form (ICF) and is able to understand the information provided in the Subject Information Sheet and ICF.
2.   Subject is at a minimum 22 years of age(inclusive).

3. Smoking, apparently healthy subject as judged by the Investigator based on all available assessments from the Screening period/Day of Admission (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, chest X-ray, and medical history).

4. Subject smokes at least 10 commercially available mCCs per day (no brand restrictions) for the last 4 weeks, based on self-reporting. Furthermore, the subject has smoked for at least the last 3 consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine ⊘200 ng/mL).

5. The subject does not plan to quit smoking in the next 6 months as assessed by the Prochaska 'Stage of Change' questionnaire.

6. The subject is ready to comply with the study protocol (e.g. readiness to accept interruptions of smoking for up to 91 days and to use THS 2.2 Menthol).

### 6.2.2 Exclusion Criteria

The exclusion criteria are:

1. As per Investigator judgment, the subject cannot participate in the study for any reason (e.g. medical, psychiatric and/or social reason).

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.

3. The subject has clinically relevant diseases which require medications (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary and cardiovascular disease or any other medical condition (including safety laboratory as per CTCAE)) , which in the opinion of the Investigator would jeopardize the safety of the subject.

4. Subject who has forced expiratory volume in 1 second/forced vital capacity ($FEV_1$/FVC) <0.7 and $FEV_1$ <80% predicted value at post-bronchodilator spirometry.

5. Subject with asthma condition ($FEV_1$/FVC <0.75 and reversibility in $FEV_1$ >12% (or > 200 mL) from pre- to post-bronchodilator values).

6. Subjects with renal insufficiency as defined by serum creatinine levels of >1.3 mg/dL for females and >1.5 mg/dL for males

7. The subject has a body mass index (BMI) <18.5 or ⊘35.0 kg/m$^2$.

8. As per Investigator judgment, the subject has medical conditions which require or will require in the course of the study a medical intervention (e.g. start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.

9. Any subject with a history of adverse events linked to caffeine or caffeine containing drugs (e.g., Vivarin), such as but not limited to hypersensitivity or allergy.

10. The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.

11. 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.

12. If a subject received any medication (prescribed or over the counter) within 14 days prior to Screening or prior to the Admission Day (Day -2) it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives or subject's safety.

13. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDS) or acetylsalicylic acid.

14. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in the study.

15. The subject has a positive urine drug test.

16. Positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B or hepatitis C.

17. Donation or receipt of whole blood or blood products within 3 months prior to Admission.

18. The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling or child).

19. 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).

20. The subject has participated in any clinical study within 3 months prior to the Screening Visit.

21. For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission), or is breast feeding.

22. For women only: Subject does not agree to use an acceptable method of contraception*.

* e.g., 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. Hysterectomy, tubal ligation, bilateral oophorectomy or post menopausal status are reasons for not needing to use birth control. Postmenopausal status is defined as women who have not experienced menses for greater than 12 months. If a woman claims she's post-menopausal, but has had her menses within 12 months, a follicle stimulating hormone test must be performed and must be within acceptable limits.

## 6.3    Product Allocation and Blinding

### 6.3.1  Methods of Assigning Subjects to Product Arms

Randomization will be conducted through the Interactive Web and Voice Response System (IXRS).

Subjects will be randomized to one of the 3 arms. Each sex and each of the current mCC consumption levels (10 to 19 mcc/day and >19 mcc/day) will have a quota applied to ensure they represent at least 40% of the total study population.

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Four separate randomization lists were provided (male smokers who smoke 10-19 mCC/day, female smokers who smoke 10-19 mCC/day, male smokers who smoke >19 mCC/day, and female smokers who smoke >19 mCC/day). Block randomization was used within each stratum (i.e. each list) in a 2:1:1 ratio (THS 2.2 Menthol:mCC:SA).

The randomization scheme will be generated by a statistical division within ▇▇▇▇▇▇ and none of the study team (Sponsor and ▇▇▇▇▇▇), investigators and study subjects will be exposed to the live randomization codes prior to randomization.

### 6.3.2 Blinding

This is an open-label study; therefore, the subjects and investigators will be unblinded to subject's product assignment after randomization. However, there will be a limited degree of blinding during the conduct of the study including the data review and data analysis process. In particular, PMI and ▇▇▇▇▇▇ personnel will be blinded to the randomized product as summarized in the following table (**Table 2: Blinding Scheme**):

## Table 2: Blinding Scheme

| Blinded Study Personnel | End of Blinding Period |
|---|---|
| PMI and ▇▇▇▇▇▇ study statisticians | After the SAP finalization or database lock[1], whichever comes last. |
| PMI study data managers | After the finalization of PMI blind database review[1]. |
| PMI safety and clinical scientist | After the finalization of PMI blind database review[1]. Can be actively un-blinded before that time point in case of the occurrence of any safety question, when appropriate. |

[1] As part of the PMI Quality Control (QC) activity, data listings will be reviewed by ▇▇▇▇▇▇ and PMI before database lock, with no access to the randomization information. Full details will be available in the data review plan.

The study scientist will be unblinded for the data review meeting, therefore the role of blinded reviewer is delegated. Any PMI and ▇▇▇▇▇▇ personnel who are not listed in the above table will be unblinded by default.

No data will be made available from the unblinded study team to blinded study team without a dummy randomization or masking in place, and any communications among the two groups will avoid the use of subject randomization information until database lock. PMI will receive blinded data for the pre-analysis data review as planned in the data review plan.

### 6.3.3 Compliance to Product Allocation

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 Menthol and mCC in THS 2.2 Menthol and mCC arms, respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each

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Tobacco Stick/mCC when requested by the subject. During the ambulatory period, the subjects randomized to the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects randomized to the SA arm will be instructed to abstain from smoking.

In addition, in subjects in the SA arm, the compliance will be chemically verified in confinement using exhaled CO breath test . The cut-off point for the CO breath test value to distinguish mCC use versus SA use will be 10 ppm (**Bennowitz et al. 2002**). No subjects from the SA arm will be withdrawn from the study if their exhaled CO breath test results are >10 ppm.

### 6.3.3.1 Dual-use

Although subjects are being requested to use solely the product/regimen allocated to them in their respective study arm, it is considered that during the ambulatory period not all subjects randomized to the THS 2.2 Menthol and SA arms might be exclusively using THS 2.2 Menthol or being abstinent at all times during the study. Subjects may concomitantly use THS 2.2 Menthol and CC (dual-use) or smoke some CC in the SA arm.

To assess dual-use of THS 2.2 Menthol and CC, PMI has defined product use categories defined by the percentage of the reported THS 2.2 Menthol Tobacco Sticks consumption during each time period of interest. The percentage use of THS 2.2 Menthol will be calculated by:

$$100 \times \frac{\text{Total number of THS 2.2 Menthol products used}}{\text{Total number of THS 2.2 Menthol products used} + \text{Total number of CC smoked (menthol and/or non-menthol)}}$$

Product use categories are summarized in **Table 25,** and **Figure 2** presents a detailed overview of the definition of the product use categories.

**Figure 2 – Product Use Pattern Categorization**
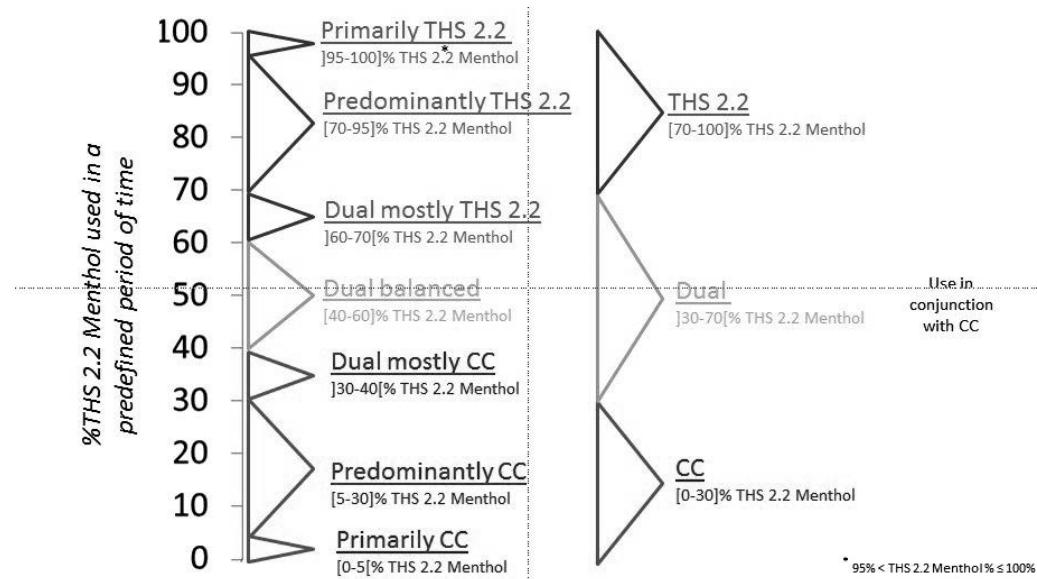


The more granular categorization scheme will be used for the definition of the PP Set and for the description of the product use patterns observed in the study whereas the less granular scheme will be used for the presentation of other study endpoints (e.g. safety endpoints) to better understand the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

### 6.3.3.2    Abstinence from mCC use

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

- "Abstinence": full abstinence from tobacco or nicotine containing product use other than the assigned product, biochemically verified with CO breath test ∷10 ppm.
- "Predominantly abstinence": not more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average and no more than two uses on a single day.
- "No abstinence": more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average or more than two uses on a single day.

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# 7    DERIVED AND COMPUTED VARIABLES

Mean change from baseline (baseline is defined in Section **12.1.4 "Definitions for Statistical Data Analysis"**) is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline.

Mean percent change from baseline is the mean of all individual subjects' percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject's baseline value and multiplying by 100. These individual subjects' percent changes from baseline values will be used to calculate the mean percent change from baseline.

When the baseline value is 0, 1 will be used in the denominator for calculating the percent change from baseline.

The QT interval corrected using Bazett's formula (QTcB) will be calculated as follows:

$$QTcB = \frac{QT}{\sqrt[2]{\left(60/HR\right)}}$$

The QT interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

Reported BMI will be calculated at site from the body weight and height using the following formula:

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

## 7.1    Biomarkers

### 7.1.1   Biomarkers of Exposure and Risk Markers in Urine

The adjustment of the urinary BoExp and Risk Markers concentration for creatinine will be calculated as:

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

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where the [ ] indicated concentrations measured from the same 24 hour urine collection or 4-hour urine fraction.

The quantity excreted for a BoExp over 24 hours will be calculated as:

$$\text{Quantity Excreted over 24 hours} = \text{Biomarker}] * \text{urine volume}$$

where the concentration and the urine volume are from the same 24 hour urine collection.

### 7.1.2  Nicotine Equivalents

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

$$
\begin{aligned}
\text{NEQ [g]} \quad = \quad & (\text{free nicotine}_c[\mu mol/l] + \text{nicotine-glucuronide}_c\,[\mu mol/l] \\
& + \text{free cotinine}_c\,[\mu mol/l] + \text{cotinine-glucuronide}_c\,[\mu mol/l] \\
& + \text{free } trans\text{-3'-hydroxycotinine}_c\,[\mu mol/l] \\
& + trans\text{-3'-ydroxycotinine-glucuronide}_c\,[\mu mol/l]) \\
& *162.2[\mu g/\mu mol]*\text{urine volume (l) / 1000 } [\mu g/mg]
\end{aligned}
$$

N.B. All concentrations must be in µmol/l before applying the above formula.

The conversion factors will be applied as follows:

| | |
|---|---|
| Free nicotine | The molecular weight is 162.232 g/mol (**Chemical Information Specialized Information Services RN:54-11-5**). Therefore to convert nicotine from ng/mL to nmol/L, the result in ng/mL is multiplied by 6.164. |
| Nicotine glucuronide | The molecular weight is 338.356 g/mol (**Chemical Information Specialized Information Services RN:152306-59-7**). Therefore to convert nicotine from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.955. |
| Cotinine | The molecular weight is 176.218g/mol (**Chemical Information Specialized Information Services RN:486-56-6**). Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 5.675. |
| Cotinine-glucuronide | The molecular weight is 352.341 g/mol (**Chemical Information Specialized Information Services RN:139427-57-9**). Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 2.838. |
| Trans-3'hydroxycotinine | The molecular weight is 192.217 g/mol (**Chemical Information Specialized Information Services RN:34834-67-8**). Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202. |

| Trans-3'hydroxycotinine-glucuronide | The molecular weight is 368.34g/mol (**Chemical Information Specialized Information Services RN:132929-88-5**). Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.715. |
|---|---|

The adjustment of NEQ for creatinine in urine will be calculated as:

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

where the concentrations are measured from the same 24 hour urine collection or 4-hour urine fraction.

### 7.1.3   CYP1A2

CYP1A2 activity is calculated as the molar metabolic ratio of PX / CAF in plasma, both expressed in molar equivalent (nmol/L).

The conversion factor will be applied as follows:

| PX | The molecular weight is 180.166 g/mol (**Chemical Information Specialized Information Services RN:611-59-6**). Therefore to convert PX in ng/mL to nmol/L the result in ng/mL is multiplied by 5.550. |
|---|---|
| CAF | The molecular weight is 194.193 g/mol. (**Chemical Information Specialized Information Services RN:58-08-2**). Therefore to convert CAF in ng/mL to nmol/L the result in ng/mL is multiplied by 5.150. |

The converted results will be calculated to three decimal places and the ratio will be reported as a percentage with two decimal places.

If either of the PX or CAF concentration is LLOQ then the ratio will not be calculated.

### 7.1.4   CYP2A6

CYP2A6 activity is calculated in plasma as the metabolic ratio of trans-3' hydroxycotinine and cotinine, both expressed in molar equivalent (nmol/L) (**Jacob et al. 2011**).

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The conversion factor will be applied as follows:

| | |
|---|---|
| Cotinine | The molecular weight is 176.215 g/mol (**Chemical Information Specialized Information Services RN:486-56-6**). Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 5.675. |
| Trans-3'hydroxycotine | The molecular weight is 192.217 g/mol (**Chemical Information Specialized Information Services RN:34834-67-8**). Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202. |

The converted results will be calculated to three decimal places and the ratio will be reported as a percentage with two decimal places.

If either of the cotinine or trans-3'hydroycotinine concentration is LLOQ then the ratio will not be calculated.

## 7.2 Pharmacokinetic Parameters

The peak nicotine and cotinine plasma concentration ($C_{peak}$) and time to peak concentration ($t_{peak}$) will be obtained directly from the concentrations taken on Day 5. If the peak concentration occurs at more than one time point then $t_{peak}$ will be assigned to the first value. The weighted average concentration over 24 hours on Day 5 ($C_{avg}$) will be calculated by dividing the area under the curve from 0 to 24 h ($AUC_{0-24\ h}$) by 24, where the $AUC_{0-24\ h}$ is calculated using the linear trapezoidal rule.

Since the samples are taken whilst the subjects are smoking freely all samples must be non-missing for the parameters to be calculated as $C_{peak}$ (and $t_{peak}$) could occur at any time.

## 7.3 Questionnaires

### 7.3.1 Socio-Economic Status Questionnaire

On Day 4, subjects will be asked a series of questions related to their education, occupational status, size and annual income of their household. These data will be used to create a measure for Socio-Economic Status (SES) that categorizes subjects into low, moderate and high SES for educational attainment, annual household income and a composite measure for educational attainment and income as detailed in **Table 3** below (**King et al., 2011**).

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**Table 3: Classification for the Socio-Economic Status Questionnaire**

| Category | Classification | Item |
|---|---|---|
| Question 1. What is the highest level of education you have completed? | Low<br><br>Moderate<br><br>High | 1 (Less than high school)<br>2 (high school graduate)<br>3-5 (some college, college graduate, advanced degree) |
| Question 2. What is your current occupational status? | Not applicable | Working now<br>Only temporarily laid off, sick leave or maternity leave<br>Looking for work, unemployed<br>Retired Disabled, permanently or temporarily<br>Keeping house<br>Student<br>Other |
| Question 3. How many people are currently living in your household? | Not applicable | Free text |
| Question 4. Of these people how many are children? | Not applicable | Free text |
| Question 5. Of these people how many are adults? | Not applicable | Free text |
| Question 6. Of the adults, how many bring income into the household? | Not applicable | Free text |
| Question 7. Which of these categories best describes your total combined family income for the past 12 months? This should include income (before taxes) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment benefits, workman's compensation, help from relatives (including child payments and alimony), and so on. | Low<br><br>Moderate<br><br>High | 1-2 (Less than $10,000 or $10,000 to $29,999)<br>3-4 ($30,000 through $44,999 or $45,000 through $59,999)<br>5-8 ($60,000 through $74,999 or $75,000 through $99,999 or $100,000 through $149,999 or $150,000 and over) |

Educational attainment will be classified as follows: if multiple answers are obtained the higher degree will be chosen; the subject cannot be classified if the answer is missing. Annual household income will be classified as follows: if multiple answers are obtained then the higher income will be chosen; the subject cannot be classified if the answer is missing or if option 9 or 10 is selected.

Education and income categories will be combined to create a composite measure for SES with the following tertile division:

- Low        Low education and Low income categories
- Moderate   Low income and Moderate education, Low income and High education, Moderate income and Low education, and High income and Low education
- High       Moderate income and Moderate education, Moderate income and High education, High income and Moderate education, and High income and High education)

Respondents who do not report either income or education will be excluded from the analysis of the composite SES.

### 7.3.2 Fagerström Test for Nicotine Dependence (FTND)

The FTND will be used in its revised version (**Heatherton et al 1991**), as updated in 2012 (**Fagerström et al. 2012**). These questions are to be answered by the subject themselves. It is conducted at Screening to determine subject's dependence on nicotine and on the Day 90 Visit to assess any changes in their dependence on nicotine.

**Table 4** describes the six questions the questionnaire consists of, and the scores associated with each question.

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

Mild       0 – 3
Moderate   4 – 6
Severe     7 – 10

### Table 4: Scoring for the Fagerstrom Test for Nicotine Dependence

| | FTND Question | Response | Score |
|---|---|---|---|
| 1 | How soon after you wake up do you smoke your first cigarette? | Within 5 minutes | 3 |
| | | 6 to 30 minutes | 2 |
| | | 31 to 60 minutes | 1 |
| | | After 60 minutes | 0 |

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## Table 4: Scoring for the Fagerstrom Test for Nicotine Dependence

| | FTND Question | Response | Score |
|---|---|---|---|
| 2 | Do you find it difficult to refrain from smoking in places where it is forbidden? | Yes | 1 |
| | | No | 0 |
| 3 | Which cigarette would you hate most to give up? | The first one in the morning | 1 |
| | | Any other | 0 |
| 4 | How many cigarettes per day do you typically smoke? | 10 or less (up to ½ pack) | 0 |
| | | 11 to 20 (a little more than ½ pack, up to a full pack) | 1 |
| | | 21 to 30 (a little more than a pack, up to 1½ packs) | 2 |
| | | 31 or more (more than 1½ packs) | 3 |
| 5 | Do you smoke more frequently during the first hours after waking than during the rest of the day? | Yes | 1 |
| | | No | 0 |
| 6 | Do you smoke if you are so ill that you are in bed most of the day? | Yes | 1 |
| | | No | 0 |

If the baseline score is 0, the percent change from baseline will be calculated using a value of 1 for the denominator.

### 7.3.3 Questionnaire of Smoking Urges-Brief (QSU-brief )

The QSU-brief (**Cox et al. 2001**) is a self-reported questionnaire completed on a daily basis from Day -1 to Day 5, and on every visit during the ambulatory period, i.e., Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90).

The QSU-brief consists of 10 items as presented in **Table 5**.

## Table 5: Questionnaire of Smoking Urges Brief - Questions and Factors

| | Question | Factor |
|---|---|---|
| 1 | I have a desire for a cigarette right now | 1 |
| 2 | Nothing would be better than smoking a cigarette right now | 2 |
| 3 | If it were possible, I probably would smoke now | 1 |
| 4 | I could control things better right now if I could smoke | 2 |
| 5 | All I want right now is a cigarette | 2 |
| 6 | I have an urge for a cigarette | 1 |
| 7 | A cigarette would taste good now | 1 |
| 8 | I would do almost anything for a cigarette now | 2 |
| 9 | Smoking would make me less depressed | 2 |
| 10 | I am going to smoke as soon as possible | 1 |

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All items will be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge to smoke.

Two factor scores and a total score will also be derived (**Cox et al. 2001**). Each factor is a subset that includes 5 of the 10 questions as defined in **Table 5**. Factor 1 represents the desire and intention to smoke with smoking perceived as rewarding, while Factor 2 represents an anticipation of relief from negative effect with an urgent desire to smoke.

The factors and total scores will be calculated by averaging non-missing item scores if at least 50% are non-missing, otherwise the factor or total score will be set to missing.

### 7.3.4    Modified Cigarette Evaluation Questionnaire

The MCEQ (**Cappelleri et al. 2007**) will be completed by the subject him/herself on a daily basis from Day -1 to Day 5 and on every ambulatory visits on Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90). On Day -1 and Day 0, all subjects will complete the questionnaire. From Day 1 onwards, only subjects who are randomized to the THS 2.2 Menthol and mCC arms will complete this questionnaire.

The MCEQ consists of 12 items as presented in **Table 6**.

### Table 6: Modified Cigarette Evaluation Questionnaire - Questions and Subscales

| | Question | Subscale |
|---|---|---|
| 1 | Was smoking satisfying? | Smoking Satisfaction |
| 2 | Did cigarettes taste good? | Smoking Satisfaction |
| 3 | Did you enjoy the sensation in your throat and chest? | Enjoyment of Respiratory Tract Sensations |
| 4 | Did smoking calm you down? | Psychological Reward |
| 5 | Did smoking make you feel more aware? | Psychological Reward |
| 6 | Did smoking make you feel less irritable? | Psychological Reward |
| 7 | Did smoking help you concentrate? | Psychological Reward |
| 8 | Did smoking reduce your hunger for food? | Psychological Reward |
| 9 | Did smoking make you dizzy? | Aversion |
| 10 | Did smoking make you nauseous? | Aversion |
| 11 | Did smoking immediately relieve your craving for a cigarette? | Craving Reduction |
| 12 | Did you enjoy smoking? | Smoking Satisfaction |

Items are assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity on that scale.

The subscales scores will be derived by averaging the individual non-missing item scores if at least 50% are non-missing, otherwise the subscale score will be set to missing.

### 7.3.5    Minnesota Nicotine Withdrawal Scale (revised edition) Questionnaire

The MNWS (**Hughes and Hatsukami 2008**) is a 24 hour recall that will be completed by the subject him/herself daily from Day 0 to Day 6, and on the second day of every visit during the ambulatory period. From Day 0 to Day 6 only, MNWS questionnaire must be asked prior to start of product use/smoking and no later than 10:00 AM. On Day 31 and Day 61 the assessment of MNWS will be conducted irrespective of the time of product use but no later than 10:00 AM. Whilst on Day 91 the assessment of MNWS has to be conducted prior to smoking but no later than 10:00 AM.

The self-reported part of the MNWS consists of the following 15 items which are rated over the last 24 hours on a scale of 0 to 4 (see **Table 7**). Higher scores indicate greater intensity on that scale.

The total scores will be derived by calculating the average of all the non-missing data from the first 9 items. If more than 50% of the first 9 items are missing then the total score will be set to missing.

### Table 7:  Minnesota Nicotine Withdrawal Scale (Revised Edition) Questionnaire Scores

| | Question | Total Score |
|---|---|---|
| 1 | Angry, irritable, frustrated. | Yes |
| 2 | Anxious, nervous. | Yes |
| 3 | Depressed mood, sad. | Yes |
| 4 | Desire or craving to smoke. | Yes |
| 5 | Difficulty concentrating. | Yes |
| 6 | Increased appetite, hungry, weight gain. | Yes |
| 7 | Insomnia, sleep problems, awakening at night. | Yes |
| 8 | Restless. | Yes |
| 9 | Impatient. | Yes |
| 10 | Constipation | No |
| 11 | Dizziness | No |
| 12 | Coughing | No |
| 13 | Dreaming or nightmares | No |
| 14 | Nausea | No |
| 15 | Sore throat | No |

### 7.3.6    Human Smoking Topography Questionnaire

Subjects will be asked by the Investigator to complete the HST questionnaire on:

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

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The HST questionnaire has 5 items rated on a 5-point scale (from strongly agree to strongly disagree). The items are:

1. The smoking of the conventional cigarettes/products is different with the device.
2. You enjoy smoking with the device as much as without it.
3. The taste of the conventional cigarettes/products is different with the device.
4. The device is easy to use.
5. Your smoking is disturbed by the device.

### 7.3.7 Cough Assessment

Subjects will be asked to assess the respiratory symptom 'cough' on a VAS, on three Likert scales, and with one open ended question on a daily basis during the confinement period (from Day 0 to Day 6), and on the second day of each ambulatory period visit (Day 30 Visit, Day 60 Visit and Day 90 Visit ). From Day 0 to Day 6, assessment of cough is done prior to start of product use/smoking and no later than 10:00 AM. On Day 31, and Day 61 assessment of cough will be conducted irrespective of the start of product use and not later than 10:00 AM. On Day 91 the assessment of cough will be conducted irrespective of the start of product use and not later than 10:00 AM.

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

The VAS will assess how bothersome cough is to the subject ranging from 'not bothering me at all' to 'extremely bothersome', and this will be given a numeric value between 0 and 100, measured on a 100mm scale.

Subjects will also be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales as presented in **Table 8**.

## Table 8 : Cough Assessment Likert Scales

| Question | Likert Scale |
|---|---|
| 1    The intensity of cough | 1 = very mild<br>2 = mild<br>3 = moderate<br>4 = severe<br>5 = very severe |
| 2    The frequency of cough | 1 = rarely<br>2 = sometimes<br>3 = fairly often<br>4 = often<br>5 = almost always |
| 3    The amount of sputum production | 0 = no sputum<br>1 = a moderate amount of sputum;<br>2 = a larger amount of sputum;<br>3 = a very large amount of sputum. |

### 7.3.8 Behavioral Risk Factor Surveillance System Questionnaire

Subjects will be assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by a standard questionnaire (Behavioral Risk Factor Surveillance System Questionnaire 2011) (**CDC, 2011**) which is validated.

The Behavioral Risk Factor Surveillance is self-administered, to be answered by subjects. The standard questionnaire consists of 5 questions. All 5 questions are close-ended questions and the responses are exhaustive and mutually exclusive. The questions are shown in **Table 9**.

### Table 9: Behavioral Risk Factor Surveillance System Questionnaire

| | Question | Responses |
|---|---|---|
| 1 | Have you smoked at least 100 cigarettes in your entire life? | Yes<br>No<br>Don't know/Not sure<br>Refused |
| 2 | Do you now smoke cigarettes every day, some days or not at all | Every day<br>Some days<br>Not at all<br>Don't know/Not sure<br>Refused |
| 3 | During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking? | Yes<br>No<br>Don't know/Not sure<br>Refused |
| 4 | How long has it been since you last smoked a cigarette, even one or two puffs? | Less than 1 month ago<br>1 month but less than 3 months ago<br>3 months but less than 6 months ago<br>6 months but less than 1 year ago 1 year but less than 5 years ago<br>5 years but less than 10 years ago<br>10 years or more<br>Don't know/Not sure<br>Refused |
| 5 | Do you currently use chewing tobacco, snuff, or snus every day, some days, or not at all | Every day<br>Some days<br>Not at all<br>Don't know/Not sure<br>Refused |

### 7.3.9 Smoking Questionnaire and Supplemental Questions

Subjects will be assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by a smoking questionnaire (SQ) which will be validated by the supplemental questions.

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The SQ is self-administrated, to be answered by subjects. The SQ focuses on self-reported current and past cigarette smoking behavior. The SQ consists of 8 questions. The first 3 questions are close-ended questions and the responses are exhaustive and mutually exclusive. The last 5 questions refer to the individual smoking history and are answered to the degree applicable. The SQ questions are shown in **Table 10**.

## Table 10: Smoking Questionnaire

| | Question | Responses |
|---|---|---|
| 1 | What is your current cigarette smoking behavior (including hand-rolled cigarettes)? | Daily smoker (at least one cigarette per day, disregarding religious fasting) Occasional smoker (less than one cigarette per day) Ex-smoker of cigarettes Non-smoker of cigarettes |
| 2 | Have you smoked at least 100 cigarettes in your entire life? | Yes No |
| 3 | Did you ever smoke cigarettes regularly, i.e. at least 1 cigarette per day? | Yes No |
| 4 | If you ever smoked cigarettes regularly: At what age did you start to smoke regularly? | Age in years |
| 5 | If you are an ex-smoker of cigarettes: For how long have you quit now? | Time in years, months and days |
| 6 | If you ever quit regular cigarette smoking: For how long did you quit altogether? | Time in years, months and days |
| 7 | What brand of cigarettes/hand-rolled tobacco did you predominantly smoke in the last 12 months of smoking? | Open question |
| 8 | On average, how many cigarettes/cigars/pipes do/did you smoke per day currently / 1 year ago / 5 years ago / 10 years ago / 15 years ago / 20 years ago / More than 20 years ago? | For each category and time point: None Less than 1 per day Actual number |

The daily CC consumption reported in these questionnaires will not be used for eligibility.

The supplemental questions consist of 8 questions which are asked by the site. The data from these questionnaires will be described as part of the CSR, but the use analysis of this data to validate the SQ will be the subject of a separate report. The supplemental questions are shown in **Table 11**:

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## Table 11: Supplemental Questions from Smoking Questionnaire

| | Question | Responses |
|---|---|---|
| 1 | How long did it take for the subject to complete the SQ? | Answer in minutes |
| 2 | Did the SQ capture your smoking behavior completely? | Yes<br>No |
| 3 | Did the SQ capture your smoking behavior correctly? | Yes<br>No |
| 4 | Did the SQ capture your smoking history completely? | Yes<br>No |
| 5 | Did the SQ capture your smoking history correctly? | Yes<br>No |
| 6 | Was the SQ self explaining? | Yes<br>No |
| 7 | Was the SQ esay to use? | Yes<br>No |
| 8 | Any comments | Open ended question |

### 7.3.10  Prochaska 'Stage of Change' Questionnaire: Intention to Quit Smoking

The Prochaska 'Stage of Change' questionnaire will be used to assess the smokers' mental state for the intention to quit (See Appendix 5 of the protocol for staging algorithm; DiClemente et al. 1991 and Velicer et al, 1995). The Prochaska 'Stage of Change' questionnaire will be performed at Screening, Day -2, Day 30 Visit, and Day 60 Visit and at Day 90 Visit. On Day -2 the Prochaska 'stage of change' questionnaire will be asked to the subject prior to product trial.

The questions are shown in **Table 12**.

## Table 12: Prochaska 'Stage of Change' Questionnaire

| | Question | Responses |
|---|---|---|
| 1 | Are you currently a smoker? | Yes<br>No: quit in last 6 months<br>No: quit more than 6 months |
| 2 | In the last year, how many times have you quit smoking for at least 24 hours? | Number of times |
| 3 | Are you seriously thinking of quitting smoking? | A) Yes, within the next 30 days<br>B) Yes, within the next 6 months<br>C) No, not thinking of quitting |

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## 7.4 Human Smoking Topography Assessment

The HST SODIM® device measures and records the flow and other per-puff parameters listed below (**Table 13**) on Days 0, 1,4 and the first day of each ambulatory visit. From the per-puff parameters, the per-cigarette parameters shown below will be derived (representing average values or totals per cigarette) (**Table 14**).

Prior to calculation of the per-cigarette parameters, the topography data will be processed through analysis software. Only data that are declared *"accepted"* by the software will contribute to the per-cigarette parameters and will be part of the study database.

### Table 13: HST- Per-Puff Parameters

| Description | Variable | Unit |
| --- | --- | --- |
| Puff number | $N_i$ | puff |
| Puff volume | $V_i$ | mL |
| Puff duration | $D_i$ | s |
| Average flow [Vi/Di] | $Q_{mi}$ | mL/s |
| Peak flow | $Q_{ci}$ | mL/s |
| Inter puff interval | $I_i$ | s |
| Sum of Ii and Di | $DF_i$ | s |
| Work [INT Pmi*FinalFlow*dt] | $W_i$ | mJ |
| Average pressure drop | $P_{mi}$ | mmWG |
| Peak pressure drop | $P_{ci}$ | mmWG |
| Average resistance [Pmi/Qmi] | $R_{mi}$ | mmWG/ml/s |
| Peak resistance [Pci/Qci] | $R_{ci}$ | mmWG/ml/s |

### Table 14: HST - Per-Cigarette Parameters

| Description | Variable | Formula | Unit |
| --- | --- | --- | --- |
| Total number of puffs | NPC | L $N_i$ | puff |
| Total puff volume | TVOL | L $V_i$ | ml |
| Average puff volume | AvgVi | L $V_i$ / NPC, i=1 ... NPC | ml |
| Average puff duration | AvgDi | L $D_i$ / NPC, i=1 ... NPC | s |
| Total puff duration | TDi | L $D_i$ | s |
| Average flow | AvgQmi | L $Q_{mi}$ / NPC, i=1 … NPC | ml/s |
| Peak flow | AvgQci | L $Q_{ci}$ / NPC, i=1 … NPC | ml/s |
| Total inter puff interval | TIi | L $I_i$ | s |
| Average inter puff interval | AvgIi | L $I_i$ / NPC, i=1 … NPC | s |

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## Table 14: HST - Per-Cigarette Parameters

| Description | Variable | Formula | Unit |
| --- | --- | --- | --- |
| Total smoking duration | TDFi | $L\,DF_i$ | s |
| Total Work | TWi | $LW_i$ | mJ |
| Average Work | AvgWi | $LW_i / NPC$, i=1 … NPC | mJ |
| Average pressure drop | AvgPmi | $LP_{mi} / NPC$, i=1 … NPC | mmWg |
| Average Peak pressure drop | AvgPci | $LP_{ci} / NPC$, i=1 … NPC | mmWg |
| Smoking Intensity | SMINT | $TVOL/TDF_i$ | ml/s |
| Puffing Time Index | PTI | $(100*TD_i)/TDFi$ | % |
| Puff Frequency | PFeq | $NPC/(TDF_i/60)$ | puff/min |

## 7.5 Categorical Variables

The categorical variables used in this study are shown below (**Table 15**). Additional categorical variables used for stratification are reported in **Table 25.**

## Table 15: Categorical Variables Definitions

| Variable | Categories | |
| --- | --- | --- |
| BMI (kg/m$^2$) | Underweight | <18.5 |
| | Normal range: | $;: 18.5$ and < 25.0 |
| | Overweight: | $;: 25.0$ and < 30.0 |
| | Obese: | $;: 30.0$ |
| FTND total score | Mild: | 0 - 3 |
| | Moderate: | 4 - 6 |
| | Severe: | 7 - 10 |
| Daily mCC consumption over the last 4 weeks as reported at Screening (per day). | 10-19 | |
| | >19 | |
| CO breath test level (ppm) | $:: 10$ | |
| | > 10 | |
| COHb level | $:: 2\%$ | |
| | > 2% | |
| Adverse event severity | Mild | |
| | Moderate | |
| | Severe | |
| Adverse event relationship | Related | |
| | Not related | |
| Adverse event expectedness | No | |
| | Yes | |
| Action taken with study product due to adverse event | Product use interrupted | |
| | Product use stopped | |
| | Product use reduced | |
| | Not applicable | |
| | None | |

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## Table 15: Categorical Variables Definitions

| Variable | Categories |
| --- | --- |
| Outcome of adverse event | Death related to adverse event |
| | Not recovered or not resolved |
| | Recovered or resolved |
| | Recovered or resolved with sequelae |
| | Recovering or resolving |
| | Unknown |
| Seriousness Criteria | Fatal |
| | Life-threatening |
| | Requires hospitalization |
| | Results in disability/incapacity |
| | Congenital anomaly/birth defect |
| Treatment given | Yes |
| | No |
| Severity of device event | Major |
| | Minor |
| Percentage use of THS 2.2 Menthol for PP Set definition | Primarily THS 2.2 (;:95-100 %) |
| | Predominantly THS 2.2 (;:70-<95%) |
| | Dual mostly THS 2.2 (;:60-<70%) |
| | Dual mostly (;:40-<60%) |
| | Dual mostly mCC (;:30-<40%) |
| | Predominantly mCC (;:5-<30%) |
| | Primarily mCC (<5%) |
| Percentage use of THS 2.2 Menthol for safety population definition | THS 2.2 (;:70-100%) |
| | Dual (;:30-<70%) |
| | mCC (<30%) |
| Compliance for the SA arm | Compliant: 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average and no more than two uses on a single day occur. |
| | Not compliant: more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average or more than two uses on a single day occur. |

## 8    SAMPLE SIZE JUSTIFICATION

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

Table 16 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 Menthol and the two control arms in COHb, 3-HPMA, MHBMA and

S-PMA on Day 5 based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study to investigate exposure to selected smoke constituents in smokers switching from CCs to smoking article (SMAR) cigarettes for 5 days, the YVD-CS01-EU study (ClinicalTrials.gov: ID: NCT00812279) sponsored by PMI. The mean ratios and CVs for SMAR/CC are expected to be the same as THS 2.2 Menthol/mCC.

**Table 16: Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC**

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

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

**Table 17** describes the expected CV and MR between THS 2.2 Menthol and the mCC control arm in Total NNAL on Day 90 based on data from a  Philip Morris USA-sponsored randomized, controlled, switching, open-label, parallel-group, single-center study in 90 male and female adult smokers evaluated six biomarkers of tobacco smoke exposure  over a 12-week period (**Frost-Pineda et al., 2008**). The mean ratios and coefficients of variations for EHCJLI /CC are expected to be the same as THS 2.2 Menthol/mCC.

**Table 17:  Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC**

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

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

**Table 18** describes the expected CV and MR between THS 2.2 Menthol and the mCC control arm in COHb, 3-HPMA, MHBMA, S-PMA based on data from a single-center, open-label, randomized, controlled, 2-arm parallel group study to evaluate the exposure to selected smoke constituents in smoking, apparently healthy subjects switching from CC to THS 2.1 compared to subjects continuing to smoke CC for 5 days, the ZRHX-EX-01 study (ClinicalTrials.gov: ID: NCT01780714) sponsored by PMI. The mean ratios and coefficients of variations for THS 2.1/CC are expected to be the same as THS 2.2 Menthol/mCC.

### Table 18: Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC

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

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

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

A minimal number of subjects are expected to be excluded from the PP Set in the confinement period.

No more than 50% of subjects are expected to be excluded from the PP Set in the THS 2.2 Menthol arm (mainly for non-compliance) and a minimal minimal number of subjects to be excluded in the CC arm in the ambulatory period. Thus the expected populations on which the reductions will be assessed as described in **Table 19**.

### Table 19: Sample Size to Assess the Reductions

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

**Table 20** describes the expected power to demonstrate a reduction on 5 primary BoExps in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and ZRHX-EX-01 and 160 smokers (~80 in THS 2.2, ~40 in CC, and ~40 in the SA arm).

**Table 20: Expected Power (YVD-CS01-EU and ZRHX-EX-01 Studies Assumptions)**

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

A total of 160 smokers (80 in THS 2.2 menthol, 40 in mCC, and 40 in the SA arm) will be randomized to demonstrate a reduction of at least 50% on 5 primary BoExp in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability.

# 9     CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

The study team was accidentally unblinded during the course of the study. The first version of the SAP was issued on 30 September 2013 prior to first subject's first visit and shared with the FDA. The list of changes from version 1.0 are listed in section 3.1. The impact of the changes on the interpretation was none and was not influenced by the unblinding.

The blinded review roles were delegated for data review. No decision on populations assignment and data review was made in an unblinded manner.

The analysis of the relationship between primary and secondary BoExp, risk markers, and NEQ is no longer an objective of the study. The impact of the study team being unblinded and making this decision was null.

Urinary BoExp, risk markers, and NEQ will be evaluated using concentration adjusted for creatinine only for the data collected from the 4-hour urine fraction. The impact of the study team being unblinded and making this decision was null.

When investigating the concordance between the results for urinary BoExp, risk markers, and NEQ in 24-hour urine collection and 4-hour urine fraction only the actual value of the concentration adjusted for creatinine will be used. The impact of the study team being unblinded and making this decision was null.

When investigating the urinary BoExp, risk markers, and NEQ in subjects quitting smoking, the 4-hour fraction data will not be used. The impact of the study team being unblinded and making this decision was null.

# 10     ANALYSIS POPULATIONS

In pivotal pharmaceutical / therapy studies the general approach is to analyze the intention-to-treat (ITT) population. In such studies the product efficacy and the product

compliance are generally highly correlated as the product effects may be detectable by the subject (e.g., relief from symptoms). Therefore, the ITT population is used to account for the effects of the product compliance. The drivers for product use (ultimately product compliance) for tobacco products are not the same as in a pharmaceutical setting. Smokers decide to smoke, despite the known risks and adverse health effects, based on social, cultural, personal, and psychological factors. Therefore the ITT approach may not be optimal in randomized studies evaluating modified risk tobacco products, as these products are targeting risk reduction which may not be the main factor influencing the choice of tobacco products used by the subjects.

The aim of this study is to demonstrate the optimal effect that could be achieved by the use of THS in terms of reduction in BoExp. The following considerations were taken into account in order to measure "optimal effect" in this study:

1. The primary analysis is designed to assess the effect in subjects who are compliant with the assigned product use, rather than the effect in the full population. The full population would represent a heterogeneous exposure (e.g., as mixed product use, or non-use of the assigned product) rather than a THS exposure.

2. The subjects are allowed to smoke the THS 2.2 Menthol product in a truly *ad libitum* setting (smoking is not restricted based on the number of CC smoked prior to study onset).

The optimal effect may be a somewhat ideal scenario, which differs from the real-world effect (effect under actual use setting) mainly by reducing the impact of non-compliance on the estimate. To be able to assess real-world effects we are planning to conduct studies, both in our clinical program (12 month exposure response studies) and in our perception and behavior program (actual use studies). In order to fully understand the full range of the potential effect THS once it is commercialized it will be important to understand both the optimal effect and the real-world effect.

The PP Set will be the primary analysis for BoExp, and risk markers. The full analysis set (FAS) will be the primary analysis set for compliance to randomization arm. Exposure and questionnaires. Exposure and questionnaires will be described by randomization arm and according to product use categories (see **Table 25**).

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

Safety will be analyzed using the safety population by randomization arm and according to product use categories (see **Table 25**).

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## 10.1      Full Analysis Set

The FAS consists of all the randomized subjects who had at least one post-randomization product use experience, if randomized to THS 2.2 Menthol or mCC, and have at least one valid non-safety assessment (THS 2.2 Menthol, mCC, and SA arms).

## 10.2      Per Protocol Set

The PP Set is a subset of the FAS and includes all randomized subjects who have no major protocol deviations impacting evaluability as defined in **Table 21** (see Section **11 "Protocol Deviations"**).

## 10.3      Safety Population

Before randomization, the safety population consists of all the subjects who had at least one exposure to THS 2.2 Menthol (including the product test at Admission Day). This also includes any randomized subjects who had no valid safety assessment post-randomization.

After the randomization, the safety population includes all randomized subjects who had at least one valid safety assessment post-randomization. Subjects in the safety populations will be analyzed according to product use categories defined over the whole ambulatory period.

## 10.4      Compliant Population

The compliant population will be a subset of the PP Set for subjects from the THS 2.2 Menthol arm who are exclusive THS 2.2 Menthol users, as defined in Section **10 "Analysis Populations"**, or for subjects from the mCC arm who are exclusive users of mCC, or for subjects in the SA arm who are abstinent, as defined in Section **6.3.3.2 "Abstinence from mCC use"**.

## 11 PROTOCOL DEVIATIONS

Protocol deviations are defined as deviations from any procedure defined in the Study Protocol, including but not limited to any violation of inclusion/exclusion criteria, mis-randomizations, use of any nicotine or tobacco-containing product other than the assigned product during each of the exposure period in confinement, assessments not performed or performed outside the scheduled time windows, or use of drugs that are known to affect CYP2A6 or CYP1A2 activity.

Information following site monitoring and other reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and subsequently recorded in an electronic data capture (EDC) system. Additional protocol deviations may be identified in the data review, these will also be recorded in the EDC system.

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Additional protocol deviations (e.g. time windows for assessments) may be identified through programatic checks and entered in ADaM datasets.

All deviations will be reviewed to determine their severity/impact when subjects are assigned to analysis populations. Each deviation will be classified as major or minor; all major deviations will be further reviewed to determine whether or not the deviation impacts the evaluability of the results and therefore should result in the subject being excluded from the PP Set.

### 11.1.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (per period of the study) to determine whether they will be excluded from any of the analysis populations. This will take place during the pre-analysis data review meeting prior to database lock. The following have been identified as the major protocol deviations.

The categories for the major deviations will include, but are not limited to the deviations presented in **Table 21**.

### Table 21: Definition of Major Protocol Deviations

| Category | Description |
| --- | --- |
| Mis-randomization | Being administered the wrong product according to the randomization schedule. |
| Mis-use of product | **Confinement:** Use of any nicotine or tobacco–containing product other than the assigned product, using the product distribution log. Exhaled CO breath test >10 ppm for subjects from the SA arm starting from Day 2. **Ambulatory:** Non-compliance in the THS 2.2 Menthol and SA arms will be defined for each period. Non-compliance is based on product use reported in the product use diary for periods 2-4, as any of the following occurrences: – Use of more than 2 CC in a single day during the period – Average product use from Day 1 in each period through the end of the period is more than 0.5 CC per day. |
| Violation | Violation of inclusion/exclusion criteria. |
| Duration of 24 hour collection | Start and end times not within the 30 min window. |

Among the above criteria, violations of inclusion criteria 1,2,3 and 4, or of the exclusion criteria 2 and 21 will be assessed for their impact on the PP Set. Any violations of other inclusion or exclusion criteria will be assessed for their impact on the PP Set and evaluated during the pre-analysis data review meeting.

### 11.1.2 Minor Protocol Deviations

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The categories for the minor deviations will include, but are not limited to the deviations presented in **Table 22**.

**Table 22: Definition of Minor Protocol Deviation Categories**

| Category | Description |
|---|---|
| Concomitant medication | Use of drugs which are known to affect CYP2A6 or CYP1A2 activity. |
| Procedural violation | Violation of planned procedure Assessments not taken at the correct time or |
| Time deviation (Questionnaires) | within the allowed time window (see **Table 23**) |
| Time deviation (Blood draws) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Time deviation (CYP1A2 activity) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Time deviation (CYP2A6) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Time deviation (Assessment of cough) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Time deviation (CO breath test) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Time deviation (Oxysterol, nasal epithelial, transcriptomics and buccal collections) | Assessments not taken at the correct time or under the correct food restrictions (see **Table 23**) |
| Time deviation (4-hour urine fraction collection) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Time deviation (HST Recording) | Assessments not taken at the correct time or within the allowed time window (see **Table 23**) |
| Visit window deviation | Day 30, Day 60 and Day 90 Visits outside of visit window (see **Table 23**). |
| Time missing | Assessment date or time is missing |
| Assessment missing | Assessment is missing |
| Visit missing | Scheduled visit not done |

### 11.1.3   Assessment Windows

During the confienment period, smoking of the randomized products should take place within the 06:30 AM and 11:00 PM window.

The assessment windows are shown in **Table 23**.

**Table 23: Assessment Windows**

| Assessment | Nominal Time point(s) | Window |
|---|---|---|
| 24 h urine sample | Start (Days -1 to 5) Start (Days 30, 60 and 90) End (Days 0 to 6) End (Days 31, 61 and 91) | 06:30 AM ± 30 min 09:00 AM ± 30 min 06:29 AM ± 30 min 08:59 AM ± 30 min |
| 4 h urine sample | Start (Day -1) Start (Day 91) End (Day -1) End (Day 91) | 10:30 AM ± 20 min Immediately after end of 24-hour urine collection 02:00 PM ± 30 min Before 02:30 PM |
| CYP1A2 activity in plasma | Day 0, Day 5 and Day 90 | 6 h after intake of caffeine tablet± 15 min |
| CYP2A6 activity | Day 0, Day 6 and Day 91 | Prior to smoking / product use |
| CO breath test | Day -2 | Time of admission to 06:30 PM Irrespective of product use |
| | Morning (Days -1 to 5) | To be done within 15 minutes prior to product use (for THS 2.2 Menthol and mCC arms) or between 08:00 AM and 09:30 AM (SA arm). |
| | Day -1 to Day 5 | Between 12: 00PM 01:30 PM, 04:00 PM and 05:30 PM, and 08:00 PM and 09:30 PM |
| | Day 6 | Prior to discharge. Irrespective of product use. |
| | Day 30 and Day 60 | Between 10:00 AM and 11:30 AM. Irrespective of product use. |
| | Day 90 | Between 10:00 AM and 12:30 AM. Irrespective of product use. |
| Assessment of Cough | Days 0 to 6 | To be done prior to product use but not later than 10:00 AM. |
| | Day 31 and Day 61 | Irrespective of product use but no later than 10:00 AM |
| | Day 91 | Prior to smoking but no later than 10:00 AM |
| MNWS questionnaire | Day 0 to 6 | To be done prior to product use but not later than 10:00 AM |

| Assessment | Nominal Time point(s) | Window |
|---|---|---|
|  | Day 31 and Day 61 | Irrespective of product use but no later than 10:00 AM |
|  | Day 91 | To be done prior to product use but no later than 10:00 AM |
| QSU-brief questionnaire | Days -1 to 5, Days 30, 60 and 90 | 08:00 PM to 11:00 PM |
| mCEQ questionnaire | Days -1 to 5, Days 30, 60 and 90 | 08:00 PM to 11:00 PM |
| Behavioral Risk Factor Questionnaire, SQ and Supplemental questions Nicotine | Days -1 and 5 | 08:00 PM to 11:00 PM |
| and cotinine in plasma | Days 0 to 4 | 08:00 PM to 09:30 PM |
|  | Day 5 for THS 2.2 Menthol and mCC arms: within 15 minutes before first product use ($T_0$): then additional blood samples at 2 hour intervals from $T_0$ until 11:00 PM. In SA arm only one blood sample between 08:00 PM to 09:30 PM | Each sample has a 5 minute time window |
|  | Day 6 for THS 2.2 Menthol and mCC arms: 20 and 24 h after $T_0$ of Day 5. In SA arm only one blood sample between 08:00 AM to 09:30 AM | 5 minute time window |
|  | Day 30 and Day 60 | 10:00 AM-11:30 AM irrespective of product use |
|  | Day 90 | 10:00 AM-12:30 PM irrespective of product use |
| COHb blood sampling | Days -1 to 4 | 08:00 PM to 09:30 PM |
|  | Morning sample on Day 5 | Within 15 minutes prior to product use (for THS 2.2 Menthol and mCC arms) or between 08:00 AM and 09:30 AM (SA arm) |
|  | Day 5 other samples | Between 12:00 PM and 01:30 PM, 04:00 PM and 05:30 PM, and 08:00 PM and 09:30 PM |
|  | Day 30 and Day 60 | Irrespective of product use between 10:00 AM and 11:30 AM. |
|  | Day 90 | Irrespective of product use |

| Assessment | Nominal Time point(s) | Window |
|---|---|---|
| | | between 10:00 AM and 12:30 AM. |
| Oxysterols and Blood sampling for bio-banking for transcriptomics | day 0, day 6 and Day 91 | Has to be done after at least 10 hours of fasting. |
| Nasal Epithelial Collectionand Buccal Collection | Day 0 and Day 90 | In the afternoon before 9:00 PM. Subject must not have eaten at least 30 minutes prior to collection |
| | Day 6 | Prior to discharge. Subject must not have eaten at least 30 minutes prior to collection |
| HST Questionnaire | Day 0 | 08:00 PM-11:00 PM |
| | Day 4, Day 30, Day 60 and Day 90 for all subjects in the THS 2.2 Menthol and mCC arms | 08:00 PM-09:30 PM |
| HST Recording | Day 0 | 06:30 AM-11:00 PM |
| | Day 1 and Day 4 for all subjects in the THS 2.2 Menthol and mCC arms smoking compatible mCC | 06:30 AM-11:00 PM |
| | Day 30, Day 60 and Day 90 for all subjects in the THS 2.2 Menthol and mCC arms smoking compatible mCC | Start time: 08:30 AM to 09:30 AM. End time: 12:30 PM to 01:30 PM. 4-hour recordings ± 15 min |
| Ambulatory Visit | Day 30, Day 60 and Day 90 Visits | ± 5 days. |

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# 12    PLANNED STATISTICAL METHODS

## 12.1    General Considerations

Data analysis will be performed using SAS® Version 9.3.

Data listings will be provided for all data collected as defined in the protocol, ordered by randomization arm and subject, Day, Visit and time point (if applicable), unless otherwise stated. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. All unscheduled assessments will be included in the listings.

### 12.1.1  Stratified Presentation

The following summaries will be produced by randomization arm, stratified by sex (male vs. female) and mCC consumption (10-19 mCC/day vs. >19 mCC/day) for the PP set at period 1 and 4:

- Demographics and Baseline Characteristics

- COHb, and MHBMA, 3-HPMA, S-PMA and total NNAL adjusted for creatinine.

- Product use

Summaries of data by product use categories will be produced for the product use time periods 1 to 4 (see **Table 25**), as appropriate.

Summaries of safety data will be provided stratified by pre-randomization and randomized period (see **Table 25**).

All endpoints will be summarized stratified by time point as appropriate.

### 12.1.2  Subgroup Analyses

No subgroup analyses will be performed in this study.

### 12.1.3  Descriptive Statistics

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), 95% confidence interval (CI), median, first and third quartiles, minimum and maximum; for log-normal data the geometric mean, geometric 95% CI and geometric coefficient of variation (CV) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will include all subject level data colected unless otherwise specified.

Unless otherwise specified, data described over time will be reported for periods 2-4 (see **Table 25**).

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Data for early termination will be summarized at the end of the corresponding period (1-4). Data for early termination collected during an unplanned ambulatory visit will be handled as specified in Section **12.1.6 "Handling of Unplanned Data"**.

Urinary BoExp Summaries
In general, urinary BoExp will be described over time as follows:
- Summary of concentration values adjusted for creatinine, and their percent change from baseline. Line graphs will be produced for arithmetic means of creatinine adjusted concentration (and 95% CI of the mean) for the percent change from baseline over all timepoints.
- Summary of quantity excreted over 24-hours values.

In general, BoExp measured in blood or breath tests will be described with summaries of the levels over time and levels expressed as percent change from baseline. BoExp levels will also be presented with line graphs.

Summaries and graphs will be produced for the FAS and PP Set. All derived variables will be listed together with the raw BoExp levels.

Safety Summaries
In general, summaries for the Safety population will be produced by randomization arm, separately for the following periods:
- Pre-Randomization, including safety data collected until randomization. Only for this period, the Safety population includes any subjects who tested the product but were not randomized and these subjects will be reported in a separate "Product Test Only" group.
- Randomized period, including Baseline and all post-Baseline data.

The following product labels will be used throughout the TFLs (**Table 24**):

**Table 24: Product Labels**

| Product | Format used in TFLs | Order in TFLs |
|---|---|---|
| Tobacco Heating System 2.2 Menthol | THSm2.2 | 1 |
| Menthol conventional cigarettes | mCC | 2 |
| Smoking abstinence | SA | 3 |

The following stratification labels (**Table 25**) for the TFLs will be used:

## Table 25: Stratification Labels

| Stratification Factor | Definition |
|---|---|
| Product preference (which product the subject would prefer to be randomized to). | THSm2.2 (THS 2.2 Menthol) mCC SA NP (No preference) |
| Sex | Male Female |
| Daily mCC consumption (per day) | 10-19 >19 |
| Safety Time Periods | Pre-Randomization period ([Product trial – Randomization]) Randomized period Confinement ([Day 1-Day 6 confinement] ) Ambulatory ([Day 6 ambulatory-Day 90 Visit]) Safety Follow-up ([Day 90 Visit – End of Study]) |
| Product Use Time Periods | Period 1 ( [Day 1-Day 6 confinement] ) Period 2 ( [Day 6 ambulatory-Day 30 Visit] ) Period 3 ( ]Day 30 Visit-Day 60 Visit] ) Period 4 ( ]Day 60 Visit-Day 90 Visit] ) |
| Product Use Categories for mCC arm | CC Only (Exclusively CC) CC Dual (Use of other products) |
| Product Use Categories for SA arm | Abstinent Predominantly Abstinent Not Abstinent |
| General Product Use Categories for THS 2.2 Menthol arm | THS 2.2 [70-100%] Dual ]30-70%[ CC [0-30%] |

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| PP SetDetailed Product use Categories for THS 2.2 Menthol | Primarily THS 2.2 (]95-100]%) Predominantly THS 2.2 ([70-95]%) Dual Mostly THS 2.2 (]60-70[%) Dual Balanced ([40-60]%) Dual Mostly CC (]30-40[%) Predominantly CC ([5-30]%) Primarily CC ([0-5[%) |

### 12.1.4  Definitions for Statistical Data Analysis

The following definitions (**Table 26**) for statistical analyses/presentations will be used:

### Table 26: Definition of Terms for the Statistical Analysis

| Term | Definition |
|------|------------|
| Baseline Value | The subject's last assessment prior to subject's first randomized product use in mCC/THS 2.2 Menthol arms. In the SA arm, the subject's last assessment prior to 10:00 AM on Day 1. |

Where the baseline is different for any of the variables measured this will be specified in the relevant section.

In this SAP, references to the Day 30 Visit, Day 60 Visit and Day 90 Visit, Day 30, Day 60, and Day 90 refer to the nominal days.

Nominal Day 31 will be refered to as the second day of the Day 30 Visit. Nominal Day 61 will be refered to as the second day of the Day 60 Visit. Nominal Day 91 will be refered to as the second day of the Day 90 Visit.

For urine collections taken on Days x to y, e.g., Days 5 to 6, these will be referred to as collected on Day x, i.e. Day 5, in the SAP.

### 12.1.5  Handling of Dropouts or Missing Data (including outside the limits of quantification)

For laboratory parameters:

- Values below the lower limit of quantification (LLOQ) will be imputed using LLOQ/2. For values above the upper limit of quantification (ULOQ), the ULOQ will be imputed.
- The number of values below LLOQ or above ULOQ will be presented in each summary table. If 50% or more data are below LLOQ or above ULOQ, only the number (%) of value below LLOQ or above ULOQ will be reported in the summaries, together with minimum and maximum of the observed values.
- Missing data at Baseline will not be imputed.

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For BoExp:

- A last observation carried forward (LOCF) approach will be implemented to replace all missing data with the last available data for each parameter being assessed.

- For parameters assessed at several timepoints during a visit, the last available data at the timepoint being assessed collected at previous study visit will be used in the analyses. For example, if on Day 5, the evening assessment (20:00-23:00) is missing for COHb, the evening assessment from Day 4 will be used for analysis regardless whether other COHb assessments are available at Day 5.

For daily product use data in safety summaries:

- Product use categories will be defined based on percentage of THS 2.2 Menthol use calculated by averaging non missing consumption data over the entire ambulatory time interval.

For daily product use data in non-safety analyses and summaries:

- If at least 75% of the daily product use assessments over a period are available, with no more than 7-days of consecutive missing data:
    o Product use categories will be defined based on percentage of THS 2.2 use calculated by averaging non missing consumption data over the analysis interval.
    o Compliance to randomized product will be defined based on the available product use data.
- If less than 75% of the daily product use assessments over a period are available, or product use data is missing over a period of more than 7 consecutive days:

    o Product use categories will be defined based on percentage of THS 2.2 use calculated by considering the missing product use data as the CC use reported at Baseline.
    o Compliance to randomized product will be defined by considering the missing product use data as the CC use reported at Baseline.

For MNWS, QSU-brief, and MCEQ questionnaire data:

- Total scores and domain or subscale scores will be derived by averaging the individual non-missing item scores if at least 50% are non-missing, otherwise they will be set to missing.

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<u>For missing or partial dates:</u>

- Missing dates for Day 30, 60, and Day 90 Visits will be imputed for the calculation of product use exposure within periods by adding 30, 60, or 90 days to the randomization date. If the imputed date falls after discharge date (e.g. for early terminated subjects), then the discharge date will be used.

- Missing or Partial dates will not be imputed for Adverse Events (AEs), for medical history, and for concomitant medications, but assumptions will be made as follows to assign them to specific analysis categories:

| Date information (*) | AE Category | Disease Category | Medication Category |
|---|---|---|---|
| Missing date or Partial date, (*e.g.*, -- May2012, or ----2011) if month/year is the same as, or later than the month and/or year of Screening. | Product-emergent | Concomitant disease | Concomitant medication |
| Partial date, (*e.g.*, --May2012, or ----2011). If month and/or year is earlier than the month and/or year of Screening. | Not product-emergent | Medical history | Prior medication |

(*) Missing or partial date refers to stop date for disease and medication categories

### 12.1.5.1 Insufficient Data for Analysis/Presentation

If there are no values or events at the general value then the break out should not be presented. For example if the number of AEs related to study procedure is zero then the presentation by severity of related events will not be produced.

Some of the TFLs will not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

For categories of summaries that have <4 subjects no summaries will be shown.

### 12.1.6 Handling of Unplanned Data

Unscheduled post-product use readings will be excluded from the summary statistics. Unscheduled readings will be labelled as unscheduled in the listings and mapped to the relative study day using the date of the study day until midnight.

### 12.1.7 Multiple Comparisons / Multiplicity

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.

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No adjustment will be made on any of the secondary endpoints.

## 12.2 Disposition of Subjects

A subject is considered:

- Enrolled if he/she was randomized or if not randomized he/she performed the product trial and he/she confirmed to be willing to use the product.
- Completed Confinement, Completed Day 30, Day 60, Day 90 Visits if he/she did not discontinue until the discharge at Day 6, Day 31, Day 61, and Day 91 respectively.

The number and percent of subjects will be summarized for the following categories: subjects screened, screening failures that tried product, screening failures that did not try product, enrolled subjects, enrolled and not randomized, randomized subjects, completed confinement, completed Day 30 Visit, completed Day 60 Visit, completed Day 90 Visit, completed study, and discontinued (if applicable discontinued subject that never used their allocated products will be identified).

Inclusion and exclusion criteria will be listed as to whether the subjects have met or not met the criteria.

All subjects who fail to complete the study will be categorized by their primary reason for discontinuation and summarized by randomization arm for the FAS. Disposition of subjects and reasons for discontinuation will also be summarized separately. Supportive listings will be provided.

The number and percent of randomized subjects with protocol deviations will be summarized by randomization arm for the PP Set and Safety Population broken down by main deviation category (major/minor), sub-categories and evaluability. Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

The number and percent of randomized subjects included in each analysis population will be summarized by randomization arm for the Safety Population. For subjects excluded from the analysis populations this will be broken down by reason for exclusion. Subjects will be counted once per exclusion, and can be counted for more than one exclusion.

Supportive listing will be provided, including any additional comments for tests that are not performed to be included on the listings of individual data.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.1.1 | Summary of Subject Disposition – All Screened Subjects |
| 15.2.1.2 | Summary of Reasons for Discontinuations – FAS |

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| TFL number | Title |
|---|---|
| 15.2.1.3.1 | Summary of Protocol Deviations – Safety Population |
| 15.2.1.3.2 | Analysis Sets and Reasons for Exclusions from Analyses |
| LISTINGS | |
| 15.3.1.1 | Listing of Inclusion/Exclusion Criteria |
| 15.3.1.8 | Listing of Subject Disposition, Randomization and Assignment to Analysis Sets |
| 15.3.1.10 | Listing of Protocol Deviations |
| 15.3.2.3 | Listing of Subject and Observations Excluded from Analysis Populations |
| 16.1.7 | Listing of Randomization Schemes and Codes |

## 12.3     Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population, FAS and for the PP Set in periods 1-4.

The demographic variables age, sex, race, body weight, height, BMI and waist circumference will be summarized by randomization arm, and by the two stratification factors (sex, and mCC consumption). Other baseline characteristics will also be included in the table.

No inferential analyses will be presented for the demographic and baseline characteristics.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP Set |
| 15.2.1.4.3.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PP Set |
| 15.2.1.4.3.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set |
| LISTINGS | |
| 15.3.1.7 | Listing of Demographics |

### 12.3.1 Current Cigarette Brand and Smoking Characteristics

The following smoking characteristics at Admission (Day -2) will be summarized and listed as specified in Section **12.3** "**Demographics and Other Baseline Characteristics**": number of mCCs smoked (categorized as 10-19 cig/day and >19 cig/day). The summaries will be presented for the Safety Population, FAS and PP Set.

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Current mCC brand(s) smoked by the subject and recorded at Screening will be summarized for the FAS. Only brands used by at least 4 subjects will be tabulated. An "other" category will contain all the brands used by less than 4 subjects. All the data at Screening and Admission (Day -2) will be listed by randomization arm and study day.

Smoking history, including whether subjects have smoked for at least the last three consecutive years and the subject's mCCs consumption during the previous 4 weeks will be listed by randomization arm at Screening and Admission (Day -2) where applicable.

Data will be listed and summarized as presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP Set |
| 15.2.1.4.3.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PP Set |
| 15.2.1.4.3.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set |
| 15.2.1.5 | Summary of Current Cigarette Brands – Safety Population |
| LISTINGS | |
| 15.3.1.2 | Listing of Current Cigarette Brands |
| 15.3.1.3 | Listing of Smoking History |

### 12.3.2    Socio-Economic Status Questionnaire

subject answers will be listed.. The number and percentage of subjects in each of the socio-economic status gradings (see Section **7.3.1** "**Socio-Economic Status Questionnaire**") will also be summarized as reported in Section **12.3** "**Demographics and Other Baseline Characteristics**", and presented in listings as shown below:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP Set |
| 15.2.1.4.3.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PP Set |
| 15.2.1.4.3.2 | Summary of Demographics and Other Baseline Characteristics by |

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| TFL number | Title |
|---|---|
| | Cigarette Consumption – PP Set |
| LISTINGS | |
| 15.3.1.11 | Listing of Socio-Economic Questionnaire Results |

### 12.3.3 Medical History and Concomitant Diseases

Medical history is defined as any condition that started and ended prior to Screening. Concomitant disease is defined as any condition that was ongoing at Screening.

Medical history and concomitant disease will be coded using MedDRA version 16.0 or later and listed separately by randomization arm, System Organ Class (SOC) and Preferred Term (PT) within SOC.

Medical History and concomitant disease will be summarized by randomization arm, SOC and PT for the Safety population.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.6 | Summary of Medical History – Safety Population |
| 15.2.1.7 | Summary of Concomitant Diseases– Safety Population |
| LISTINGS | |
| 15.3.1.9 | Listing of Medical History and Concomitant Diseases |

### 12.3.4 Other Data

Other data collected at Screening and/or Admission will be listed by randomization arm. These data are as follows:

- Cotinine urine test
- Urine pregnancy test
- Chest x-ray
- Urine drug screen
- Serology
- Alcohol breath test
- Prior medication
- Willingness to use THS 2.2 Menthol products.
- Product preference question

Prior Medication will be listed as described in Section **12.6.4.4.1** "**Prior and Concomitant Medication**".

Product preference will be collected at Admission (Day -2) and states the product which the subject prefers to be randomized to (THS 2.2 Menthol, mCC, SA or No preference).

Data will be summarized by randomization arms along with Baseline characteristics.Willingness and ability to use the product will be included in the disposition summary table for all screened subjects.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.1.1 | Summary of Subject Disposition – All Screened Subjects |
| LISTINGS | |
| 15.3.1.4 | Listing of Product test and Willingness to Use the Product |
| 15.3.1.5 | Listing of Product Preference |
| 15.3.1.6 | Listing of Safety Laboratory Entry Criteria |
| 15.3.6.4 | Listing of Prior and Concomitant Medication |

## 12.4    Measurements of Product Compliance

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

Levels of CO in exhaled breath will be measured in the SA arm to ensure that the subjects have not smoked any cigarettes. This will serve as a compliance tool starting from Day 2, because of possible carry over effect. These data (continuous and categorical) will be summarized and listed by product use category (**Table 25**) in the SA arm.

During the ambulatory period, subjects in the 3 study arms will capture, from the time of Discharge on Day 6 to Day 90, the number of product used (e.g., menthol and non-menthol CC, Menthol Tobacco Sticks, or any other tobacco /nicotine-containing products including NRT) on a daily basis in the product use electronic diary. The product use electronic diary will serve as a compliance tool in the 3 arms. On Day 6, the compliance to the product will be ensured using both the accountability log (from 06:30 AM to time of discharge) and the product use electronic diary (filled from the time of Discharge on Day 6 to Day 90).

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.5.1 | Summary of Compliance as Measured by Exhaled CO (ppm) During Confinement Period - FAS in the SA Arm |
| 15.2.5.2 | Summary Of Compliance by Period and Overall - FAS |
| LISTINGS | |
| 15.3.3.2 | Listing of Bood, Plasma, Serum, and Exhaled Air Biomarkers |
| 15.3.2.1.1 | Listing of Product Usage (CC) During Confinement Period |

| TFL number | Title |
|---|---|
| 15.3.2.1.2 | Listing of Product Usage (THSm2.2) During Confinement Period |
| 15.3.2.1.3 | Listing of Product Usage During Ambulatory Period |

## 12.5   Extent of Exposure (Product Consumption)

Details of the product test prior to enrollment and of product use after randomization will be listed and summarized. During the confinement period the daily usage as recorded in the log will be summarized by randomization arm.

The maximum and average daily usage of the assigned product and non-assigned product will be summarized over the whole ambulatory period, as recorded by the subject, and for each of the periods 2 to 4 (see section **10.2 "Per Protocol Set"**).

All summaries will be produced for the Safety Population, and for the PP Set at periods 1 to 4. Summaries of data in Ambulatory will also be repeated for the FAS, if the population differs from the Safety population by more than 10%.

In addition the number and percentage of subjects falling into each product use category (see Section **6.3.3.1 "Dual-use"**) during the ambulatory period will be presented.

The average product use data will also be presented by randomized product and by product use categorization (see Section **6.3.3.1 "Dual-use"**).

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.2.1.1 | Summary of Daily Product Use in Confinement Period – FAS |
| 15.2.2.1.2 | Summary of Daily Product Use in Confinement Period – PP Set |
| 15.2.2.2 | Summary of Maximum Daily Product Use in Ambulatory Period – FAS |
| 15.2.2.3.1 | Summary of Average Daily Product Use in Ambulatory Period – FAS |
| 15.2.2.3.2 | Summary of Average Daily Product Use in Ambulatory Period – PP Set |
| 15.2.2.4 | Summary of Product Use by Product Use Category in Ambulatory Period – FAS |

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| TFL number | Title |
|---|---|
| 15.2.2.5.1 | Summary of Average Daily Product Use by Product Use Category in Ambulatory Period – FAS |
| 15.2.2.5.2 | Summary of Average Daily Product Use by Product Use Category in Ambulatory Period – PP Set |
| LISTINGS | |
| 15.3.2.1.1 | Listing of Product Usage (CC) During Confinement Period |
| 15.3.2.1.2 | Listing of Product Usage (THSm2.2) During Confinement Period |
| 15.3.2.1.3 | Listing of Product Usage During Ambulatory Period |
| 15.3.2.2 | Listing of THS 2.2 Menthol Device Details |

## 12.6  Planned Statistical Analyses

For all statistical analysis data from all arms, THS 2.2 Menthol, mCC and SA will be included in all models as appropriate.

### 12.6.1  Primary Analyses

#### 12.6.1.1 Analysis of Biomarkers of Exposure for Primary Endpoints

The BoExp (COHb in blood and urinary concentrations of MHBMA, 3-HPMA, S-PMA and Total NNAL) used for the primary analysis will be summarized as detailed in Section **12.1.3** "**Descriptive Statistics**". The listing of the COHb data will have a flag for whether a subject's COHb was <2%.

The baseline is as defined in Section **12.1.4** "**Definitions for Statistical Data Analysis**".

The primary endpoints will be log-transformed (base$_e$) prior to analysis. The analysis will compare the evening COHb level (20:00-21:30 PM) on Day 5; and urinary concentrations of MHBMA, 3-HPMA and S-PMA ajusted for creatinine on Day 5 and urinary concentrations of Total NNAL adjusted for creatinine on Day 90 Visit between the THS 2.2 Menthol and mCC arms for the PP Set. An analysis of covariance (ANCOVA) (**Snedecor and Cochran 1982**) model will be used with terms for the log-transformed baseline value, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm.

The SAS code to be used for the THS 2.2 Menthol and mCC data is shown below:

```
Proc glm data=_data_;
Class randomization_arm sex cigarette_cons;
Model   log_biomarker   =   log_baseline   sex   cigarette_cons
randomization_arm;
Lsmean randomization_arm / pdiff =control('mCC') alpha=0.05 cl;
Run;
```

The least squares (LS) means and estimate of the difference and the 95% CI will be back-transformed.The geometric LS means for each randomization arm along with the ratio

(THS 2.2 Menthol : mCC), two-sided 95% CI and one-sided p-value will be presented in the tables. THS 2.2 menthol : mCC effects will be graphed in a forest plot.

All figures, summaries and analyses will be performed on the PP Set. Additional descriptive statistics will be provided within the secondary analysis.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.1.1 | Forest Plot of Statistical Analysis of Biomarkers of Exposure on Day 5 and Day 90 – PP Set |
| 15.1.1.2 | Biomarkers of Exposure Geometric Mean and 95% CI – PP Set |
| | |
| TABLES | |
| 15.2.3.1.1 | Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective – PP Set |
| 15.2.4.1.1 | Descriptive Statistics of Blood COHb (%) – PP Set |
| 15.2.4.1.1.1 | Descriptive Statistics of Blood COHb (%) by Sex – PP Set |
| 15.2.4.1.1.2 | Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – PP Set |
| 15.2.4.2.1 | Descriptive Statistics of MHBMA in 24-hour Urine Collection – PP Set |
| 15.2.4.2.1.1 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set |
| 15.2.4.2.1.2 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set |
| 15.2.4.3.1 | Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – PP Set |
| 15.2.4.3.1.1 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set |
| 15.2.4.3.1.2 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set |
| 15.2.4.4.1 | Descriptive Statistics of S-PMA in 24-hour Urine Collection – PP Set |
| 15.2.4.4.1.1 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set |
| 15.2.4.4.1.2 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set |

| TFL number | Title |
| --- | --- |
| 15.2.4.5.1 | Descriptive Statistics of Total NNAL in 24-hour Urine Collection – PP Set |
| 15.2.4.5.1.1 | Descriptive Statistics of Total NNAL Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set |
| 15.2.4.5.1.2 | Descriptive Statistics of Total NNAL Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set |
| LISTINGS | |
| 15.3.3.1 | Listing of Urinary Biomarkers |
| 15.3.3.2 | Listing of Bood, Plasma, Serum, and Exhaled Air Biomarkers |

### 12.6.1.2 Confirmatory Analysis

The hypothesis to be tested is that the geometric mean level of the BoExp for THS 2.2 Menthol is lower relative to mCC and will be as described in Section **12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Endpoints"**.

### 12.6.1.3 Sensitivity Analysis

As a sensitivity analysis, the ANCOVA model described in Section **12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Endpoints"** will be repeated for the PP Set at Day 5 and Day 90 data by means of a mixed model approach, without the LOCF data imputation described in Section **12.1.5 "Handling of Dropouts or Missing Data (including outside the limits of quantification)"**. Any data outside of the allowed time window (see **Table 23: Assessment Windows**) on Days 5 and 90 will be excluded from the analysis.

The SAS code to be used for the THS 2.2 Menthol and mCC data is shown below:

```
Proc mixed data=_data_;
Class randomization_arm sex cigarette_cons;
Model   log_biomarker   =   log_baseline   sex   cigarette_cons
randomization_arm;
Lsmean randomization_arm / pdiff =control('mCC') alpha=0.05 cl;
Run;
```

An additional sensitivity analysis will be produced for the primary analysis, summaries and graphs of the COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL will be repeated for the compliant population for THS 2.2 Menthol vs mCC. The analysis will use the same model as described in Section **12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Endpoints"**

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.1.3 | Biomarkers of Exposure Geometric Mean and 95% CI – Compliant Population |
| TABLES | |
| 15.2.3.1.2 | Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective using Mixed Model – PP Set |
| 15.2.3.1.3 | Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective – Compliant Population |
| 15.2.4.1.3 | Descriptive Statistics of Blood COHb (%) – Compliant Population |
| 15.2.4.2.3 | Descriptive Statistics of MHBMA in 24-hour Urine Collection – Compliant Population |
| 15.2.4.3.3 | Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – Compliant Population |
| 15.2.4.4.3 | Descriptive Statistics of S-PMA in 24-hour Urine Collection – Compliant Population |
| 15.2.4.5.3 | Descriptive Statistics of Total NNAL in 24-hour Urine Collection – Compliant Population |

### 12.6.2 Secondary Analyses

The analysis of COHb, MHBMA, 3-HPMA, and S-PMA at Day 90 and Total NNAL at Day 5 will be repeated for the PP Set.

The analysis of the COHb, MHBMA, 3-HPMA, S-PMA at Day 5/ Day 90 and Total NNAL at Day 90 will be repeated for the FAS as described in Section **12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Endpoints"**. These endpoints will also be examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as for the primary analysis for the PP Set.

The baseline is for the biomarkers measured in urine is as defined in Section **12.1.4** "**Definitions for Statistical Data Analysis**".

#### 12.6.2.1 Analysis of Biomarkers of Exposure for Secondary Endpoints

The BoExp for the secondary endpoints are exhaled CO and total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, Total NNAL and NEQ (all analysed from a 24-hour urine collection) at Day 5 and Day 90 will be described as reported in Section **12.1.3** "**Descriptive Statistics**". Urine parameters will be analyzed as concentrations adjusted for creatinine and the quantity excreted in urine over 24 hours. In addition the quantity excreted in urine over 24 hours for MHBMA, 3-HPMA, S-PMA and Total NNAL will also be presented as above.

All BoExp apart from CO breath test will be analyzed in the log scale.

BoExp will be analyzed using the same model described in Section **12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Endpoints"**. No adjustment will be made for multiple comparisons. For all BoExp, if the results from the Day 5 analysis are significant (one-sided p-value $\therefore 0.025$) then the statistical significance will be evaluated for the results of the analysis at Day 90 values. LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables. Forest plots of the ratios and 95% CI will also be produced.

BoExp will also be examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as above for the PP Set. In addition, the sensitivity analyses described in Section **12.6.1.3 "Sensitivity Analysis"** for the biomarkers of exposure for primary objectives will be repeated for the biomarkers of exposure for secondary objectives.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.1.2 | Biomarkers of Exposure Geometric Mean and 95% CI – PP Set |
| 15.1.1.4 | Biomarkers of Exposure Geometric Mean and 95% CI – FAS |
| TABLES | |
| 15.2.3.2 | Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5/90 Visit versus mCC and SA for the Secondary Objective – PP Set. |
| 15.2.3.3 | Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5/90 Visit versus mCC and SA for the Secondary Objective – FAS. |
| 15.2.3.4 | Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit– PP Set. |
| 15.2.3.5 | Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit– FAS. |
| 15.2.3.6 | Sensitivity Analysis of Additional Biomarkers of Exposure versus mCC and SA using Mixed Model on Day 5/90 Visit – PP Set |
| 15.2.3.7 | Sensitivity Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit– Compliant Population |
| 15.2.4.1.2 | Descriptive Statistics of Blood COHb (%) – FAS |
| 15.2.4.1.3 | Descriptive Statistics of Blood COHb (%) – Compliant Population |
| 15.2.4.2.2 | Descriptive Statistics of MHBMA in 24-hour Urine Collection – FAS |
| 15.2.4.2.3 | Descriptive Statistics of MHBMA in 24-hour Urine Collection – Compliant Population |

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| TFL number | Title |
|---|---|
| 15.2.4.3.2 | Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – FAS |
| 15.2.4.3.3 | Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – Compliant Population |
| 15.2.4.4.2 | Descriptive Statistics of S-PMA in 24-hour Urine Collection – FAS |
| 15.2.4.4.3 | Descriptive Statistics of S-PMA in 24-hour Urine Collection – Compliant Population |
| 15.2.4.5.2 | Descriptive Statistics of Total NNAL in 24-hour Urine Collection – FAS |
| 15.2.4.5.3 | Descriptive Statistics of Total NNAL in 24-hour Urine Collection – Compliant Population |
| 15.2.4.6.1 | Descriptive Statistics of Exhaled CO (ppm) – PP Set |
| 15.2.4.6.2 | Descriptive Statistics of Exhaled CO (ppm) – FAS |
| 15.2.4.7.1 | Descriptive Statistics of 1-OHP in 24-hour Urine Collection – PP Set |
| 15.2.4.7.2 | Descriptive Statistics of 1-OHP in 24-hour Urine Collection – FAS |
| 15.2.4.8.1 | Descriptive Statistics of Total NNN in 24-hour Urine Collection – PP Set |
| 15.2.4.8.2 | Descriptive Statistics of Total NNN in 24-hour Urine Collection – FAS |
| 15.2.4.9.1 | Descriptive Statistics of 4-ABP in 24-hour Urine Collection – PP Set |
| 15.2.4.9.2 | Descriptive Statistics of 4-ABP in 24-hour Urine Collection – FAS |
| 15.2.4.10.1 | Descriptive Statistics of 1-NA in 24-hour Urine Collection – PP Set |
| 15.2.4.10.2 | Descriptive Statistics of 1-NA in 24-hour Urine Collection – FAS |
| 15.2.4.11.1 | Descriptive Statistics of 2-NA in 24-hour Urine Collection – PP Set |
| 15.2.4.11.2 | Descriptive Statistics of 2-NA in 24-hour Urine Collection – FAS |
| 15.2.4.12.1 | Descriptive Statistics of o-tol in 24-hour Urine Collection – PP Set |
| 15.2.4.12.2 | Descriptive Statistics of o-tol in 24-hour Urine Collection – FAS |
| 15.2.4.13.1 | Descriptive Statistics of CEMA in 24-hour Urine Collection – PP Set |
| 15.2.4.13.2 | Descriptive Statistics of CEMA in 24-hour Urine Collection – FAS |
| 15.2.4.14.1 | Descriptive Statistics of HEMA in 24-hour Urine Collection – PP Set |

| TFL number | Title |
|---|---|
| 15.2.4.14.2 | Descriptive Statistics of HEMA in 24-hour Urine Collection – FAS |
| 15.2.4.15.1 | Descriptive Statistics of B[a]P in 24-hour Urine Collection – PP Set |
| 15.2.4.15.2 | Descriptive Statistics of B[a]P in 24-hour Urine Collection – FAS |
| 15.2.4.16.1 | Descriptive Statistics of HMPMA in 24-hour Urine Collection – PP Set |
| 15.2.4.16.2 | Descriptive Statistics of HMPMA in 24-hour Urine Collection – FAS |
| 15.2.4.17.1 | Descriptive Statistics of S-BMA in 24-hour Urine Collection – PP Set |
| 15.2.4.17.2 | Descriptive Statistics of S-BMA in 24-hour Urine Collection – FAS |
| 15.2.4.18.1 | Descriptive Statistics of NEQ in 24-hour Urine Collection – PP Set |
| 15.2.4.18.2 | Descriptive Statistics of NEQ in 24-hour Urine Collection – FAS |
| | |
| LISTINGS | |
| 15.3.3.1 | Listing of Urinary Biomarkers |
| 15.3.3.2 | Listing of Bood, Plasma, Serum, and Exhaled Air Biomarkers |

### 12.6.2.2 Nicotine and Cotinine Concentrations

The concentrations of nicotine and cotinine will be listed and summarized. During confinement, the evening concentration levels at 08:00 PM is considered. Baseline is the assessment at 08:00 PM to 09:30 PM on Day 0. Line graphs of the nicotine and cotinine concentration profiles across all study days showing mean and 95% CI will also be produced.

Nicotine and cotinine concentrations at each post-baseline timepoint separately will be analysed in the log space using an ANCOVA model with terms for log-transformed baseline concentration, sex, average daily mCC consumption over the last 4 weeks as reported during screening, and product. No adjustment will be made for multiple comparisons.

The SAS code described in Section **12.6.1.3** "**Sensitivity Analysis**" will be used for the analysis of nicotine and cotinine.

Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the PP Set and FAS by randomization arm.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.1.1 | Plasma Nicotine and Cotinine Profile (ng/mL) over the 90 Days Geometric Mean and 95% CI – PP Set |
| 15.1.2.1.2 | Plasma Nicotine and Cotinine Profile (ng/mL) over the 90 Days Geometric Mean and 95% CI – FAS |
| TABLES | |
| 15.2.4.19.1 | Descriptive Statistics of Plasma Nicotine and Cotinine Concentrations (ng/mL) – PP Set |
| 15.2.4.19.2 | Descriptive Statistics of Plasma Nicotine and Cotinine Concentrations (ng/mL) – FAS |
| 15.2.4.20.1 | Analysis of Plasma Nicotine and Cotinine Concentrations (ng/mL) over the 90 Days – PP Set |
| 15.2.4.20.2 | Analysis of Plasma Nicotine and Cotinine Concentrations (ng/mL) over the 90 Days – FAS |
| LISTINGS | |
| 15.3.3.3 | Listing of Plasma Nicotine and Cotinine Concentrations |

### 12.6.2.3 Nicotine and Cotinine Pharmacokinetic Parameters

The parameters $C_{peak}$, $C_{avg}$ and $t_{peak}$ will be calculated on Day 5 as described in Section **7.2** "**Pharmacokinetic Parameters**". The data will be listed and summarized for both nicotine and cotinine.

The analysis will compare the log-transformed $C_{peak}$ and $C_{avg}$ on Day 5 between the THS 2.2 Menthol and mCC arms. An analysis of variance (ANOVA) model will be used with terms for sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm.

The SAS code will be similar to that described in Section **12.6.1.3** "**Sensitivity Analysis**", with no baseline value being included in the model.

LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables.

For $t_{peak}$ on Day 5 the comparison between the THS 2.2 Menthol and mCC arms will be made by the Wilcoxon Rank Sum test using PROC NPAR1WAY in SAS. Median difference and 95% CI using the Hodges-Lehmann estimate will be tabulated.

The following code will be used:

```
Proc npar1way data=_data_ hl median;
Class randomization_arm;
Var tpeak;
Run;
```

All summaries and analyses will be performed on the PP Set and FAS.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.4.21.1 | Descriptive Statistics of Plasma Nicotine and Cotinine PK Parameters on Day 5 – PP Set |
| 15.2.4.21.2 | Descriptive Statistics of Plasma Nicotine and Cotinine PK Parameters on Day 5 – FAS |
| 15.2.4.22.1 | Analysis of Plasma Nicotine and Cotinine PK Parameters on Day 5 – PP Set |
| 15.2.4.22.2 | Analysis of Plasma Nicotine and Cotinine PK Parameters on Day 5 – FAS |
| LISTINGS | |
| 15.3.3.4 | Listing of Plasma Nicotine and Cotinine Pharmacokinetic Parameters on Day 5 |

### 12.6.2.4 CYP1A2 Activity

CYP1A2 activity will be measured in plasma on Day 0, Day 5 and Day 90. In this study the CYP1A2 activity will be calculated using the molar ratio of PX and CAF, as described in Section **7.1.3 "CYP1A2"**. Descriptive statistics of the values and percent change on Days 5 and 90 from Day 0 and supportive listings will be provided.

The analysis will compare the log-transformed Day 5 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms. ANCOVA models will be used on CYP1A2 activity levels with terms for log-transformed baseline, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm. No adjustment will be made for multiple comparisons. If the results from the Day 5 analysis are significant (one-sided p-value $\therefore 0.025$) then the statistical significance will be repeated for the analysis at the Day 90 values. The SAS code will be similar to that described in Section **12.6.1.3 "Sensitivity Analysis"**.

Geometric LS means for each product along with the ratio (THS 2.2 Menthol :mCC) and 95% CI will be presented in the tables.

CYP1A2 activity will also be examined to compare the observed reductions in THS 2.2 Menthol vs. SA using the same methodology as above.

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If there are any CYP1A2 assessments performed within 5 half-lives since the use of a concomitant medication affecting CYP1A2 activity, the analysis will be repeated by excluding these assessments for both the PP Set and FAS

All summaries and analyses will be performed on the FAS and PP Set.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.4.23.1 | Descriptive Statistics of CYP1A2 Activity (%) – PP Set |
| 15.2.4.23.1.1 | Descriptive Statistics of CYP1A2 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP1A2 Activity – PP Set |
| 15.2.4.23.2 | Descriptive Statistics of CYP1A2 Activity (%) – FAS |
| 15.2.4.23.2.1 | Descriptive Statistics of CYP1A2 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP1A2 Activity – FAS |
| 15.2.4.24.1 | Analysis of CYP1A2 Activity (%) – PP Set |
| 15.2.4.24.1.1 | Analysis of CYP1A2 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP1A2 Activity – PP Set |
| 15.2.4.24.2 | Analysis of CYP1A2 Activity (%) – FAS |
| 15.2.4.24.2.1 | Analysis of CYP1A2 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP1A2 Activity – FAS |
| LISTINGS | |
| 15.3.4.1 | Listing of CYP1A2 Activity and Changes from Baseline |

### 12.6.2.5 Risk Markers

The risk markers are:

- Systolic and diastolic blood pressure on Day 0, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, and TC in serum on Day 0, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Fibrinogen in plasma on Day 0, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- HbA1c in blood on Day 0 and Day 90 Visit.
- sICAM-1 in serum on Day 0, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- WBC and platelet count in blood on Day 0, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-PGF2$a$ and 11-DTX-B2 in 24 hour urine on Day 0, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).

- Body weight and waist circumference on Day -2 and Day 90 Visit.

The results along with the changes from baseline will be listed and summarized. In addition line graphs will be produced for product means (and 95% CI) over all timepoints.

The analysis will compare the results on Day 90 between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms for the FAS and PP set. An ANCOVA model will be used with terms for Baseline, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm. No adjustment will be made for multiple comparisons.

Blood pressure, HbA1c, LDL, HDL, TG, TC, WBC, body weight and waist circumference will be analyzed in the regular scale. 8-epi-PGF2$a$, 11-DTX-B2, sICAM will be analyzed in the logarithmic scale. Other risk markers will be logarithmically transformed prior to analysis if there is evidence of non-normality by means of Shapiro-Wilks test.

The SAS code will be the same as described in Section **12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Endpoints"**.

LS means for each product along with the difference (THS 2.2 Menthol - mCC) or ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables along with a forest plot of the results.

If there are any 11-DTX-B2 assessments performed within 5 half-lives since the use of a concomitant medication affecting the production of 11-DTX-B2, the analysis will be repeated by excluding these assessments for both the PP Set and FAS

All tables, figures and analyses will be produced for the FAS and PP Set. Figures will be produced for the PP Set.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.2.2 | Forest Plot of Statistical Analysis of Risk Markers – PP Set |
| 15.1.2.3.1 | Risk Markers Mean and 95% CI – PP Set |
| 15.1.2.3.2 | Risk Markers Mean and 95% CI – FAS |
| TABLES | |
| 15.2.4.25.1 | Analysis of Risk Markers – PP Set |
| 15.2.4.25.1.1 | Analysis of 11-DTX-B2 (units) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting 11-DTX-B2 Production – PP Set |
| 15.2.4.25.2 | Analysis of Risk Markers – FAS |
| 15.2.4.25.2.1 | Analysis of 11-DTX-B2 (units) Excluding Assessments within 5 |

| TFL number | Title |
|---|---|
| | Half-Lives of a Concomitant Medication Affecting 11-DTX-B2 Production – FAS |
| 15.2.4.26.1 | Descriptive Statistics of Blood Pressure (mmHg) – PP Set |
| 15.2.4.26.2 | Descriptive Statistics of Blood Pressure (mmHg) – FAS 15.2.4.27.1 Descriptive Statistics of hs-CRP (units), homocysteine (units), blood glucose (units), LDL (units), HDL (units), TG (units), and TC (units) – PP Set |
| 15.2.4.27.2 | Descriptive Statistics of hs-CRP (units), homocysteine (units), blood glucose (units), LDL (units), HDL (units), TG (units), and TC (units) – FAS |
| 15.2.4.28.1 | Descriptive Statistics of Fibrinogen (units) – PP Set |
| 15.2.4.28.2 | Descriptive Statistics of Fibrinogen (units) – FAS |
| 15.2.4.29.1 | Descriptive Statistics of HbA1c (units) – PP Set |
| 15.2.4.29.2 | Descriptive Statistics of HbA1c (units) – FAS |
| 15.2.4.30.1 | Descriptive Statistics of sICAM (units) – PP Set |
| 15.2.4.30.2 | Descriptive Statistics of sICAM (units) – FAS |
| 15.2.4.31.1 | Descriptive Statistics of Total WBC Count (units), Neutrophils Counts (units), Basophils Counts (Units), Eosinophils Counts (units), Lymphocytes Counts (units), Monocytes Counts (units) and Platelet Count (units) – PP Set |
| 15.2.4.31.2 | Descriptive Statistics of Total Total WBC Count (units), Neutrophils Counts (units), Basophils Counts (Units), Eosinophils Counts (units), Lymphocytes Counts (units), Monocytes Counts (units) and Platelet Count (units) – FAS |
| 15.2.4.32.1 | Descriptive Statistics of 8-epi-PGF2$a$ (units) and 11-DTX-B2 (units) – PP Set |
| 15.2.4.32.1.1 | Descriptive Statistics of 11-DTX-B2 (units) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting 11-DTX-B2 Production – PP Set |
| 15.2.4.32.2 | Descriptive Statistics of 8-epi-PGF2$a$ (units) and 11-DTX-B2 (units) – FAS |
| 15.2.4.32.2.1 | Descriptive Statistics of 11-DTX-B2 (units) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting 11-DTX-B2 Production – FAS |
| 15.2.4.33.1 | Descriptive Statistics of Body weight (kg) and waist circumference (cm) – PP Set |
| 15.2.4.33.2 | Descriptive Statistics of Body weight (kg) and waist circumference (cm) – FAS |

| TFL number | Title |
|---|---|
| LISTINGS | |
| 15.3.3.1 | Listing of Urinary Biomarkers |
| 15.3.3.2 | Listing of Bood, Plasma, Serum, and Exhaled Air Biomarkers |
| 15.3.6.6 | Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.7 | Listing of Hematology Data Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.9 | Listing of Vital Signs Data and Changes from Baseline |

## 12.6.3 Exploratory Analysis

### 12.6.3.1 Biomarkers of Exposure in 4 hour fraction

The BoExp MHBMA, 3-HPMA, S-PMA, Total NNAL, total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, and NEQ (all analysed from a 4 hour fraction) at Day -1 and Day 91 will be described as reported in Section **12.1.3** "**Descriptive Statistics**". The parameters will be analyzed as concentration adjusted for creatinine.

All BoExp will be analyzed in the log-scale.

BoExp on Day 90 will be analyzed using the same model described in Section **12.6.1.1** "**Analysis of Biomarkers of Exposure for Primary Endpoints**". No adjustment will be made for multiple comparisons. LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables.

BoExp will also be examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as above for the PP Set.

All figures, summaries and analyses will be performed on the PP Set and presented in an Appendix of the CSR.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.34 | Analysis of Biomarkers of Exposure in 4-hour Fraction versus mCC and SA on Day 90 Visit– PP Set |
| 15.2.4.35 | Descriptive Statistics of MHBMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.36 | Descriptive Statistics of 3-HPMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.37 | Descriptive Statistics of S-PMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.38 | Descriptive Statistics of Total NNAL in 4-hour Urine Fraction – PP Set |
| 15.2.4.39 | Descriptive Statistics of 1-OHP in 4-hour Urine Fraction – PP Set |
| 15.2.4.40 | Descriptive Statistics of Total NNN in 4-hour Urine Fraction – PP Set |

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| TFL number | Title |
|---|---|
| 15.2.4.41 | Descriptive Statistics of 4-ABP in 4-hour Urine Fraction – PP Set |
| 15.2.4.42 | Descriptive Statistics of 1-NA in 4-hour Urine Fraction – PP Set |
| 15.2.4.43 | Descriptive Statistics of 2-NA in 4-hour Urine Fraction – PP Set |
| 15.2.4.44 | Descriptive Statistics of o-toluidine in 4-hour Urine Fraction – PP Set |
| 15.2.4.45 | Descriptive Statistics of CEMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.46 | Descriptive Statistics of HEMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.47 | Descriptive Statistics of B[a]P in 4-hour Urine Fraction – PP Set |
| 15.2.4.48 | Descriptive Statistics of HMPMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.49 | Descriptive Statistics of S-BMA in 4-hour Urine Fraction – PP Set |
| 15.2.4.50 | Descriptive Statistics of NEQ in 4-hour Urine Fraction – PP Set |
| LISTINGS | |
| 15.3.3.5 | Listing of Biomarkers of Exposure in 4-hour Urine Fraction |

### 12.6.3.2 Questionnaires

### 12.6.3.2.1 FTND Questionnaire

The FTND questionnaire will be administered at Screening and the Day 90 Visit.

FTND score value and the number and percentage of subjects in each category (mild/moderate/severe) will be presented at Screening and Day 90 Visit. The change from Screening in the FTND score at Day 90 will also be presented. The changes in the categories will also be presented in a shift table.

All summaries and shift tables will be performed on the PP, FAS and Compliant populations.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP Set |
| 15.2.1.4.3.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PP Set |
| 15.2.1.4.3.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set |
| 15.2.4.51.1 | Descriptive Statistics of Fagerström Test for Nicotine Dependence Results – PP Set |
| 15.2.4.51.2 | Descriptive Statistics of Fagerström Test for Nicotine Dependence Results – FAS |
| 15.2.4.51.3 | Descriptive Statistics of Fagerström Test for Nicotine Dependence Results – Compliant Population |

| TFL number | Title |
|---|---|
| LISTINGS | |
| 15.3.6.13 | Listing of Fagerström Test for Nicotine Dependence Results |

**12.6.3.2.2 Urge-to-Smoke Questionnaire of Smoking Urges Brief**

The QSU-brief will be administered daily from Days -1 to 5, and Days 30, 60 and 90. The change from baseline will be calculated for the total score and the two domain scores (relief and reward). The total score and two domain scores, along with the percent change from baseline will be summarized. The answers to the individual questions, along with the domain scores, total scores, changes and percent changes from baseline will be listed.

The profiles of the raw means from baseline to Day 90 Visit for the total score and two domain scores will be produced.

The analysis will be performed separately for each post-baseline timepoint in the domain and total scores. An ANCOVA model will be used with terms for baseline QSU-BRIEF score, sex, average daily mCC consumption over the last 4 weeks as reported during screening, and randomization arm. No adjustment will be made for multiple comparisons. The SAS code to be used is similar to the model reported in Section **12.6.1.3 "Sensitivity Analysis"**, amended as appropriate to obtain the required comparisons.

LS means for each randomization_arm along with the difference (THS 2.2 Menthol - mCC) and (THS 2.2 Menthol – SA) with 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the PP Set and the FAS.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.4.1 | QSU-brief Total Scores Arithmetic Mean and 95% CI – PP Set |
| 15.1.2.4.2 | QSU-brief Total Scores Arithmetic Mean and 95% CI – FAS |
| 15.1.2.5.1 | QSU-brief Total Scores Least Squares Means Differences and 95% CI – PP Set |
| 15.1.2.5.2 | QSU-brief Total Scores Least Squares Means Differences and 95% CI – FAS |
| TABLES | |
| 15.2.4.52.1 | Descriptive Statistics of QSU-brief Factors and Total Scores – PP Set |
| 15.2.4.52.2 | Descriptive Statistics of QSU-brief Factors and Total Scores – FAS |
| 15.2.4.53.1 | Analysis of QSU-brief Factors and Total Scores – PP Set |
| 15.2.4.53.2 | Analysis of QSU-brief Factors and Total Scores – FAS |
| LISTINGS | |

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| TFL number | Title |
|---|---|
| 15.3.6.14 | Listing of QSU-brief Questionnaire Results and Changes from Baseline |

### 12.6.3.2.3 Modified Cigarette Evaluation Questionnaire

The mCEQ will be administered daily from Days -1 to 5, and Days 30 Visit, 60 Visit and 90 Visit. All summaries, profiles and analysis will be presented for the THS 2.2 Menthol and mCC only. The mCEQ is not captured for the SA arm.

The domain scores, along with the percent change from baseline will be summarized. The answers to the individual questions, along with the domain scores, changes and percent changes from Baseline will be listed.

The profiles of the raw means from baseline to Day 90 for the five subcale scores will be produced.

The analysis will be performed separately for each post-baseline timepoint in the subscales. An ANCOVA model will be used with terms for baseline mCEQ score, sex, and average daily mCC consumption over the last 4 weeks as reported during screening, and randomization arm. No adjustment will be made for multiple comparisons.

The SAS code to be used is similar to the model reported in Section **12.6.1.3 "Sensitivity Analysis"**.

LS means for each product along with the difference (THS 2.2 Menthol - mCC) with 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the PP Set and the FAS.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.6.1 | MCEQ Subscales Arithmetic Mean and 95% CI – PP Set |
| 15.1.2.6.2 | MCEQ Subscales Arithmetic Mean and 95% CI – FAS |
| 15.1.2.7.1 | MCEQ Subscales Least Squares Means Differences and 95% CI – PP Set |
| 15.1.2.7.2 | MCEQ Subscales Least Squares Means Differences and 95% CI – FAS |
| TABLES | |
| 15.2.4.54.1 | Descriptive Statistics of MCEQ Subscales – PP Set |
| 15.2.4.54.2 | Descriptive Statistics of MCEQ Subscales – FAS |
| 15.2.4.55.1 | Analysis of MCEQ Subscales – PP Set |
| 15.2.4.55.2 | Analysis of MCEQ Subscales – FAS |
| LISTINGS | |
| 15.3.6.16 | Listing of MCEQ Questionnaire Results and Changes from Baseline |

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**12.6.3.2.4 Minnesota Nicotine Withdrawal Questionnaire**

The MNWS will be administered daily from Days 0 to 6, and Days 31, 61 and 91 for the assessment of Day-1 to Day 5, and Days 30, 60 and 90 as it is a 24-hour recall questionnaire.

All summaries, profiles and analysis will be presented for the THS 2.2 Menthol, mCC and SA arms.

The total score, along with the percent change from baseline will be summarized. The answers to the individual questions, along with the total score, the changes and percent changes from baseline will be listed.

The profiles of the raw means from baseline to Day 90 for the total scores will be plotted.

The analysis will compare each post baseline timpoint separately for the total score. An ANCOVA model will be used with terms for baseline score, sex, average daily mCC consumption over the last 4 weeks as reported during screening, and randomization arm,. No adjustment will be made for multiple comparisons.

The SAS code to be used is similar to the model reported in Section **12.6.1.3 "Sensitivity Analysis"**.

LS means for each product along with the difference (THS 2.2 Menthol - mCC) and (THS 2.2 Menthol – SA) with 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the PP Set and FAS only.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.8.1 | MNWS Total Score Arithmetic Mean and 95% CI – PP Set |
| 15.1.2.8.2 | MNWS Total Score Arithmetic Mean and 95% CI – FAS |
| 15.1.2.9.1 | MNWS Total Score Arithmetic Least Squares Means and 95% CI – PP Set |
| 15.1.2.9.2 | MNWS Total Score Arithmetic Least Squares Means and 95% CI – FAS |
| TABLES | |
| 15.2.4.56.1 | Descriptive Statistics of MNWS Total Score – PP Set |
| 15.2.4.56.2 | Descriptive Statistics of MNWS Total Score – FAS |
| 15.2.4.57.1 | Analysis of MNWS Total Score – PP Set |
| 15.2.4.57.2 | Analysis of MNWS Total Score – FAS |
| LISTINGS | |
| 15.3.6.15 | Listing of MNWS Questionnaire Results and Changes from Baseline |

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### 12.6.3.2.5 Human Smoking Topography Questionnaire

The HST questionnaire will be administered on Days 0, 4, 30, 60 and 90.

The number and percentage of subjects in each category of the items of the questionnaire will be summarized. The individual responses will be listed.

All summaries will be performed on the PP Set.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.4.58 | Descriptive Statistics of HST Questionnaire Data – PP Set |
| LISTINGS | |
| 15.3.7.2 | Listing of HST Questionnaire Results |

### 12.6.3.2.6 Risk Factor Surveillance System Questionnaire

The Risk Factor Surveillance System Questionnaire will be administered on Day -1 and Day 5.

The individual responses will be listed only.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| LISTINGS | |
| 15.3.6.17 | Listing of Risk Factor Surveillance System Questionnaire Results |

### 12.6.3.2.7 Smoking Questionnaire and Supplemental Questions

The SQ and supplemental questions will be administered on Days -1 and 5.

The individual responses will be listed only.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| LISTINGS | |
| 15.3.6.18 | Listing of Smoking Questionnaire and Supplemental Questions Results |

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**12.6.3.2.8 Prochaska 'Stage of Change' Questionnaire**

The Prochaska 'stage of change' questionnaire will be administered at Screening, Day -2, Day 30, Day 60 and Day 90.

The Prochaska 'Stage of Change' Questionnaire Results will be summarized on the FAS and Compliant Population. The individual responses will be listed.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.4.59.1 | Descriptive Statistics of Prochaska 'Stage of Change' Questionnaire Results – FAS |
| 15.2.4.59.2 | Descriptive Statistics of Prochaska 'Stage of Change' Questionnaire Results – Compliant Population |
| LISTINGS | |
| 15.3.6.19 | Listing of Prochaska 'Stage of Change' Questionnaire Results |

### 12.6.3.3 Human Smoking Topography Parameters

The HST assessments will take place on Day 0, Day 1, Day 4, Day 30, Day 60 and Day 90 in the THS 2.2 Menthol and mCC arms only, if mCC are compatible with the HST SODIM® device. On Day 0, Day 1 and Day 4 the HST will be conducted on each product use. On Day 30, Day 60 and Day 90 the HST will be recorded over a 4-hour period only.

The per puff parameters are shown in **Table 13** and the per cigarette parameters are shown in **Table 14**.

The per-cigarette parameters derived from the HST assessments will be averaged per day and summarized along with their changes from baseline. The per-puff and per-cigarette parameters will be listed. In addition the randomization arm mean and 95% CI per cigarette parameters will be presented graphically.

The averaged per-cigarette parameters will be anlysed on Days 1, 4, 30 , 60 and 90 separately using an ANCOVA model with terms for baseline score, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm. No adjustment will be made for multiple comparisons.

The SAS code to be used is similar to the model reported in Section **12.6.1.3 "Sensitivity Analysis"**.

LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the PP Set only.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.10 | HST Parameters Averaged Over the Visit Arithmetic Mean and 95% CI – PP Set |
| TABLES | |
| 15.2.4.60 | Descriptive Statistics of HST Parameters per Cigarette – PP Set |
| 15.2.4.61 | Analysis of HST Parameters per Cigarette – PP Set |
| LISTINGS | |
| 15.3.7.1 | Listing of HST Assessments and Changes from Baseline |

### 12.6.3.4 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Day 0, Day 6 and Day 91. In this study the CYP2A6 activity will be calculated using the metabolic ratio of trans 3' hydroxycotinine and cotinine, as described in Section **7.1.4 "CYP2A6"**. Descriptive statistics of the values and changes on Day 6 and Day 91 from Day 0 and supportive listings will be provided.

The analysis will compare the log-transformed Day 6 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms. ANCOVA models will be used with terms for log-transformed baseline, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm. No adjustment will be made for multiple comparisons. If the results from the Day 6 analysis are significant (one-sided p-value $::0.025$) then the statistical significance will be repeated for the analysis at the Day 91 values. The SAS code to be used is similar to the model reported in Section **12.6.1.3 "Sensitivity Analysis"**.

Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables

CYP2A6 activity will also be examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as above.

If there are any CYP2A6 assessments performed within 5 half-lives since the use of a concomitant medication affecting CYP2A6 activity, the analysis will be repeated by excluding these assessments for both the PP Set and FAS

All summaries and analyses will be performed on the FAS and PP Set.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.62.1 | Descriptive Statistics of CYP2A6 Activity (%) – PP Set |
| 15.2.4.62.1.1 | Descriptive Statistics of CYP2A6 Activity (%) Excluding Assessments |

| TFL number | Title |
|---|---|
| | within 5 Half-Lives of a Concomitant Medication Affecting CYP2A6 Activity - PP Set |
| 15.2.4.62.2 | Descriptive Statistics of CYP2A6 Activity (%) – FAS |
| 15.2.4.62.2.1 | Descriptive Statistics of CYP2A6 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP2A6 Activity - FAS |
| 15.2.4.63.1 | Analysis of CYP2A6 Activity (%) – PP Set |
| 15.2.4.63.1.1 | Analysis of CYP2A6 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP2A6 Activity – PP Set |
| 15.2.4.63.2 | Analysis of CYP2A6 Activity (%) – FAS |
| 15.2.4.63.2.1 | Analysis of CYP2A6 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP2A6 Activity – FAS |
| LISTINGS | |
| 15.3.6.20 | Listing of CYP2A6 Activity and Changes from Baseline |

### 12.6.3.5 Ames Mutagenicity Test

The 24 hour urine collection for the Ame's mutagenicity test will be on Day 0, Day 5 and Day 90.

Descriptive statistics of the values and percent changes on Day 5 and Day 90 from baseline of the YG1024+S9 mutagenicity will be provided, along with listings.

All summaries will be performed on the FAS, and PP Set.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.64.1 | Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (units) – PP Set |
| 15.2.4.64.2 | Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (units) – FAS |
| LISTINGS | |
| 15.3.5.1 | Listing of Ames Mutagenicity Results and Changes from Baseline |

### 12.6.3.6 Visual Inspection of the Tobacco Plugs

The collection of the tobacco plugs from the THS 2.2 Menthol products will be performed on Days 1 to 5, and Days 30, 60 and 90. The number and percentage of tobacco plugs showing each of the following criteria will be summarized by day: "No overheating", "White spot(s) inside the tobacco plug", "Ashes inside the tobacco plug and burnt paper" and "Missing".

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All summaries will be performed on the FAS only.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.4.65 | Descriptive Statistics of Visual Inspection of the THS 2.2 Menthol Tobacco Plugs Data – FAS |
| LISTINGS | |
| 15.3.6.21 | Listing of Visual Inspection of the Tobacco Plugs |

### 12.6.3.7 Oxysterols

Plasma concentrations of 6*a*-hydroxy-5*a*-cholestane, 7*a*-hydroxycholesterol, 5*a*,6*a*-epoxycholestanol, 7-ketocholesterol, 7�hydroxycholesterol, 5�6�epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, TC, 22(R)-hydroxycholesterol and 4ß-hydroxycholesterol will be measured in plasma on Day 0, Day 6 and Day 90 Visit (2nd Day).

Descriptive statistics of the values and changes on Day 6 and Day 91 from Day 0 and supportive listings will be provided.

All summaries and figures will be performed on the FAS and PP Set.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.2.11.1 | Oxysterol Parameters Arithmetic Mean and 95% CI – PP Set |
| 15.1.2.11.2 | Oxysterol Parameters Arithmetic Mean and 95% CI – FAS |
| TABLES | |
| 15.2.4.66.1 | Descriptive Statistics of Oxysterol Parameters – PP Set |
| 15.2.4.66.2 | Descriptive Statistics of Oxysterol Parameters – FAS |
| LISTINGS | |
| 15.3.6.22 | Listing of Oxysterol Data and Changes from Baseline |

### 12.6.3.8 Product preference analysis

The product preference as asked at admission will serve as a sensitivity analysis for the product exposure.

All summaries will be produced for the Safety populations.

These data will also be presented categorized separately by product preference and by product use categorization (see Section **6.3.3.1 "Dual-use"**).

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The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.4.67 | Descriptive Statistics of Average Daily Product Use in Ambulatory Period by Preferred Product Declared at Admission – FAS |
| 15.2.4.68 | Descriptive Statistics of Product Use Categories by Preferred Product Declared at Admission – FAS |
| LISTINGS | |
| 15.3.1.5 | Listing of Product Preference Results |

### 12.6.3.9 Concordance Between 24-hour Urine Collection and 4-hour Urine Fraction

The concordance will be investigated between MHBMA, 3-HPMA, S-PMA, total NNAL, total 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ, 8-epi-PGF2$a$ and 11-DTX-B2 (expressed as concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4- hour urine fraction) at baseline and at Day 90 Visit.

Scatterplots between each pair of variables will be produced showing the Spearman Rank correlation coefficient on the plot. In adition Bland-Altman (**Altman and Bland 1983**) plots of the data will be produced including the mean of the differences and the 95% CI. These will be produced for the FAS and presented in an Appendix of the CSR.

In these scatterplots the data from the 24-hour urine collection will be on the x-axis.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.2.12.1 | ScatterPlot of Urinary MHBMA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.12.2 | Bland-Altman Plot for Concordance of Urinary MHBMA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.13.1 | ScatterPlot of Urinary 3-HPMA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.13.2 | Bland-Altman Plot for Concordance of Urinary 3-HPMA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.14.1 | ScatterPlot of Urinary S-PMA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |

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| TFL number | Title |
|---|---|
| 15.1.2.14.2 | Bland-Altman Plot for Concordance of Urinary S-PMA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.15.1 | ScatterPlot of Urinary Total NNAL Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.15.2 | Bland-Altman Plot for Concordance of Urinary Total NNAL Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.16.1 | ScatterPlot of Urinary Total 1-OHP Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.16.2 | Bland-Altman Plot for Concordance of Urinary Total 1-OHP Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.17.1 | ScatterPlot of Urinary Total NNN Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.17.2 | Bland-Altman Plot for Concordance of Urinary Total NNN Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.18.1 | ScatterPlot of Urinary 4-ABP Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.18.2 | Bland-Altman Plot for Concordance of Urinary 4-ABP Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.19.1 | ScatterPlot of Urinary 1-NA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.19.2 | Bland-Altman Plot for Concordance of Urinary 1-NA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.20.1 | ScatterPlot of Urinary 2-NA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.20.2 | Bland-Altman Plot for Concordance of Urinary 2-NA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.21.1 | ScatterPlot of Urinary o-toluidine Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.21.2 | Bland-Altman Plot for Concordance of Urinary o-toluidine Concentration Adjusted for Creatinine from 24 hour Urine Collection |

| TFL number | Title |
|---|---|
| | and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.22.1 | ScatterPlot of Urinary CEMA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.22.2 | Bland-Altman Plot for Concordance of Urinary CEMA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.23.1 | ScatterPlot of Urinary HEMA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.23.2 | Bland-Altman Plot for Concordance of Urinary HEMA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.24.1 | ScatterPlot of Urinary B[a]P Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.24.2 | Bland-Altman Plot for Concordance of Urinary B[a]P Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.25.1 | ScatterPlot of Urinary HMPMA Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.25.2 | Bland-Altman Plot for Concordance of Urinary HMPMA Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.26.1 | ScatterPlot of Urinary NEQ Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.26.2 | Bland-Altman Plot for Concordance of Urinary NEQ Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.27.1 | ScatterPlot of Urinary 8-epi-PGF2$a$ Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.27.2 | Bland-Altman Plot for Concordance of Urinary 8-epi-PGF2$a$ Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.28.1 | ScatterPlot of Urinary 11-DTX-B2 Concentration Adjusted for Creatinine from 24 hour Urine Collection versus 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |
| 15.1.2.28.2 | Bland-Altman Plot for Concordance of Urinary 11-DTX-B2 Concentration Adjusted for Creatinine from 24 hour Urine Collection and 4 hour Urine Fraction at Baseline and Day 90 Visit – FAS |

### 12.6.3.10 BoExp in Subjects Quitting Smoking

The data to be followed for subjects who quit smoking are:

CO (ppm) in exhaled breath, COHb in blood (%), Urinary BoExp and NEQ (expressed as quantity excreted and concentration adjusted for creatinine) in 24 hour urine collection, hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, HbA1c, sICAM-1, total white blood cell count, platelet count, 8-epi-PGF2*a* and 11-DTX-B2.

These data will be plotted and summarized versus time since quitting for all subjects who quit smoking. The time since quitting will be rounded up to the nearest 30 days, such that a subject who quits before the Day 30 Visit will be assumed to have quit smoking for 30 days at the Day 30 Visit, 60 days at the Day 60 Visit and 90 days at the Day 90 Visit. Similarly a subject who quits smoking between the Day 30 Visit and the Day 60 Visit will be assumed to have quit smoking for 30 days at the Day 60 Visit and 60 days at the Day 90 Visit, and a subject who quits smoking between the Day 60 Visit and the Day 90 Visit will be assumed to have quit smoking for 30 days at the Day 90 Visit.

The data will be presented in the below outputs if more than 5 subjects quit smoking in the THS 2.2 Menthol or MCC arm in a separate Appendix of the CSR.

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.29 | Biomarkers of Exposure and Risk Markers in Subjects who Quit Smoking vs. Time Since Quitting Smoking Arithmetic Mean and 95% CI – Subjects Quitting THS and CC |
| TABLES | |
| 15.2.4.69 | Descriptive Statistics of Biomarkers of Exposure and Risk Markers in Subjects who Quit Smoking Summarized by Time Since Quitting Smoking – Subjects Quitting THS and CC |

## 12.6.4 Safety Evaluation

Safety variables monitored in this study include: AEs; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; concomitant medication, clinical chemistry, hematology, urine analysis safety panel, BMI, physical examination, respiratory symptoms (cough assessment).

### 12.6.4.1 Safety Reporting

The primary analysis of Safety parameters will be conducted on the Safety Population as described in Section **12.1.3** "**Descriptive statistics**".

### 12.6.4.2 Adverse Events

A product emergent AE is defined as an AE that occurs after first product use or that is present prior to first product use and becomes more severe after first product use. All other AEs will not be summarized but provided in listings only.

All AEs occurring from the signing of informed consent will be recorded electronically. However, only product emergent AEs will be summarized. The AE listings will include all AEs captured in the database at any time during the study (including those from subjects who were not in the safety population).

In general, AE summary tables reporting the number of events and the number and percentage of subjects reporting at least one AE will be produced by randomization arm for the Pre-Randomization and Randomized periods, as reported in Section **12.6.4.1** "**Safety Reporting**". AE data during the Randomized period will also be presented stratified by Confinement, Ambulatory, and Safety Follow-up.

Ambulatory AE data will also be reported by product use category (see **Table 25**) defined on product use over the whole ambulatory period. In particular, the general product use categories for THS 2.2 will be used, and the [Predominantly Abstinence] and [Smoking Abstinence] categories will be presented for THS 2.2 Menthol and mCC arm if at least one subject is associated to these categories.

### 12.6.4.2.1 All Adverse Events

A general summary table of AEs will be presented including:

- The number of events and the number and percentage of subjects reporting at least one AE.
- The number of events and the number and percentage of subjects reporting at least one study product –related AE, broken down by product relatedness (related to THS 2.2 Menthol/ mCC) and expectedness (expected for THS 2.2 Menthol / mCC).
- The number of events and the number and percentage of subjects reporting at least one AE broken down by severity including each subject only once with his worst severity.
- The number of events and the number and percentage of subjects reporting at least one SAE.
- The number of events and the number and percentage of subjects reporting at least one AE leading to any action taken, broken down by action taken related to the product (product use interrupted, product use reduced, product use stopped, not applicable, none), treatment given (yes, no), study discontinuation, other action taken.
- The number of events and the number and percentage of subjects reporting at least one AE related to study procedure

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Additional summary tables of AEs will be presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by SOC and PT coded according to the MedDRA dictionary (version 16.0).

If a subject has more than one occurrence of the same AE, the subject will be counted only once within a PT with the worst occurrence based on the presentation (e.g., for presentation by severity = most severe, for presentation by relationship = most related). Missing information on the intensity of AE will be counted as severe.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.1 | Summary of Adverse Events– Safety Population |
| 15.2.6.2 | Summary of Adverse Events by Product Use Category in Ambulatory Period – Safety Population |
| 15.2.6.3 | Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.3.1 | Summary of Adverse Events (Incidence >5% in any Study Arm) by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.4 | Summary of Adverse Events by Product Use Category, System Organ Class and Preferred Term – Safety Population |
| 15.2.6.5 | Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population |
| 15.2.6.6 | Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population |
| 15.2.6.7 | Summary of Adverse Events Leading to Study Product Discontinuation, Interruption, or Reduction by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.8 | Summary of Adverse Events Leading to Study Product Discontinuation, Interruption, or Reduction by Product Use Category, System Organ Class and Preferred Term – Safety Population |
| 15.2.6.9 | Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.10 | Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.11 | Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Severity – Safety Population |
| LISTINGS | |
| 15.3.6.1 | Listing of Adverse Events |

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### 12.6.4.2.2 Serious Adverse Events (Including Deaths)

A summary table of SAEs will be presented using the same approach as for AEs (see Section **12.6.4.2** "**Adverse Events**"), and including the number of events and the number and percentage of subjects reporting at least one SAE broken down by seriousness criteria (fatal, life-threatening, requires hospitalization, results in disability/incapacity, congenital anomaly/birth defect).

SAEs will also be listed in separate listings by product.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.12 | Summary of Serious Adverse Events by System Organ Class and Preferred Term – Safety Population |
| LISTINGS | |
| 15.3.6.2 | Listing of Serious Adverse Events |

### 12.6.4.2.3 Adverse Events Leading to Discontinuation

Summaries will be presented for AEs leading to discontinuation, by product as described in Section **12.6.4.2** "**Adverse Events**",

AEs leading to discontinuation will also be listed in separate listings by product.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.13 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.14 | Summary of Adverse Events Leading to Study Discontinuation by Product Use Category, System Organ Class and Preferred Term – Safety Population |
| LISTINGS | |
| 15.3.6.3 | Listing of Adverse Events Leading to Study Discontinuation |

### 12.6.4.2.4 Laboratory Abnormalities

The shift in toxicity grades from baseline to worst grade recorded while in the exposure period will be presented in tables for the clinical chemistry, hematology and urinalysis parameters. Details related to the toxicity grading of laboratory abnormalities are available in Section **12.6.4.3** "**Clinical laboratory Evaluation**".

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.16 | Summary of Clinical Chemistry Parameters – Safety Population |
| 15.2.6.17 | Summary of Hematology Parameters – Safety Population |
| 15.2.6.18 | Summary of Urinalysis Parameters – Safety Population |

### 12.6.4.2.5 THS2.2 Menthol Device Events

All events relating to the device type will be listed for each subject, including event description, device type the event relates to, severity of event, AE relationship, proposed solution and onset/stop dates/times. Device events will be classified according to PMI controlled terminology.

A summary table of device events will be presented by product, including:

- Number of device events and the number and percentage of subjects reporting at least one device event.
- Number of device events and the number and percentage of subjects categorized by severity of device event (minor, major)
- Number of device events and the number and percentage of subjects categorized by AE relationship (related, not related)
- Number of device events and the number and percentage of subjects categorized by event description (Cigarette Holder (CH) stops heating, CH does not charge, CH led blinking red, Smoking experience does not start, electronic malfunction, other)

Device events and inventory will be listed by product. Data collected during Screening will be listed but not summarized.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.15 | Summary of THS 2.2 Menthol Device Events – Safety Population |
| LISTINGS | |
| 15.3.6.5 | Listing of THS 2.2 Menthol Device Events and Malfunctions |

### 12.6.4.3 Clinical Laboratory Evaluation

**Table 27** below lists the hematology, clinical chemistry and urine analysis parameters to be assessed in this study.

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## Table 27: List of Laboratory Safety Parameters

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

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the principal investigator (PI) and assessed for clinical relevance. If the PI 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. If the condition worsens from screening to after product-use it will be recorded as an AE.

The grading scheme used in the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] version 4.03) will be used by the PI to assess abnormal laboratory values. These CTCAE grades will be derived programmatically in the creation of the datasets.

Laboratory data will be summarized and listed at Screening and Day 0 for the Pre-Randomization period; and at Baseline, Day of Discharge (Day 6), Day 30 Visit, Day 60 Visit and Day 90 Visit for the Randomized period data together with changes from Baseline. The number and percentage of subjects with normal results, high/low results and abnormal clinical significant result (as defined by PI comment),and CTCAE toxicity grading will be tabulated for laboratory parameters, together with shift in normality (Normal, Abnormal NCS, Abnromal CS) and in CTCAE toxicity grading from Baseline.

Listings for the clinical laboratory data will include the following information: change from Baseline, normal/ high/low (with respect to the reference range), abnormal clinically significant (as defined by the PI comments) and shift from Baseline, the PI comments, the CTCAE grade and the shift in CTCAE grade. Only CTCAE grades greater than zero will be presented.

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The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.16 | Summary of Clinical Chemistry Parameters – Safety Population |
| 15.2.6.17 | Summary of Hematology Parameters – Safety Population |
| 15.2.6.18 | Summary of Urinalysis Parameters – Safety Population |
| LISTINGS | |
| 15.3.6.6 | Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.7 | Listing of Hematology Data Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.8 | Listing of Urinalysis Data Shift, Changes from Baseline and CTCAE grades |

### 12.6.4.4 Vital Signs, Physical Findings and Other Observations Related to Safety

### 12.6.4.4.1 Prior and Concomitant Medication

Prior medication is defined as any medication that started and ended prior to Screening. Concomitant medication is defined as any medication starting on or after Screening. Medications that started prior to Screening and are ongoing at Screening are considered as concomitant.

All medications will be listed by product using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization-Drug Dictionary Enhanced [WHO-DDE] Q1 2012). A flag will be presented on the listing indicating whether the medication is prior or concomitant. Prior and concomitant medications will be listed by randomization arm. Concomitant medications will be summarized by randomization arm for the Safety population showing the number and percent of subjects who used the medication at least once by ATC 1st and 2nd levels and preferred drug name.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.19.1 | Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population |
| 15.2.6.19.2 | Summary of Concomitant Medication by Preferred Drug Name – Safety Population |
| LISTINGS | |
| 15.3.6.4 | Listing of Prior and Concomitant Medication |

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**12.6.4.4.2 Physical Examination**

Physical examination data recorded at the Screening visit, Admission (Day -2), Day of discharge (Day 6), Day 30 Visit, Day 60 Visit and Day 90 Visit will be listed by product. Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. The number of subjects (%) with normal, abnormal and abnormal clinically significant results will be tabulated by body systems for the Randomized period at Baseline, day of discharge, Day 30 Visit, Day 60 Visit and Day 90 Visit, including shifts in normality from Baseline.

Body weight and waist circumference recorded at Admission (Day -2), Day of discharge from Confinement (Day 6), Day 30 Visit, Day 60 Visit and Day 90 Visit; and body height recorded at the Screening visit will also be listed together with BMI. Descriptive statistics of body weight, waist circumference, body height and BMI (BMI will also be categorized as shown in Section **7.5** "**Categorical Variables**"), at Admission and Day of discharge will be presented.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.23 | Summary of Physical Examination of Body Systems – Safety Population |
| 15.2.6.24 | Summary of Weight, Waist Circumference and BMI Results – Safety Population |
| LISTINGS | |
| 15.3.6.12 | Listing of Physical Examination Findings, Shift and Changes from Baseline |

**12.6.4.4.3 Vital Signs**

Systolic and diastolic blood pressure, pulse rate and respiratory rate measured during the study will be listed by study visit, including low/normal/high results.

Descriptive statistics will be presented for supine systolic and supine diastolic blood pressure, pulse rate and respiratory rate at baseline, and on every subsequent day of both the confinement and ambulatory periods by product for each study day. Vital signs data will be summarized together with changes from baseline.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | TABLES |
| 15.2.6.20 | Summary of Supine Vital Signs – Safety Population |
| LISTINGS | LISTINGS |
| 15.3.6.9 | Listing of Vital Signs Data and Changes from Baseline |

**12.6.4.4.4 Full Lung Function Data**

Lung function parameters assessed during the study include:

- DLCO.
- KCO.
- $FEV_1$.
- FVC.
- VC expressed as L.
- TLC.
- FRV.
- IC.
- Mid expiratory flow (25-75)
- Measurement interpretation (categories: normal, abnormal, abnormal clinically significant)

The above data are collected at Screening, Day 0, Day of discharge from Confinement (Day 6) and Day 90 Visit. At Screening, data are collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator. All other spirometry assessments are performed without bronchodilator.

Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set (**Hu and Cassano, 2000**). Spirometry data values and normality evaluation will be listed by randomization arm and study day. Assessments performed after Baseline will be listed together with change from Baseline and shift in normality. Spirometry data from subjects who had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for DLCO, KCO, $FEV_1$(L), $FEV_1$ (% pred), FVC(L), FVC(% pred), $FEV_1$/FVC, VC, TLC, FRV, IC, mid expiratory flow (25-75) at Baseline (pre or without bronchodilator), Day of Discharge from Confinement (Day 6), and Day 90 Visit by randomization arm, and overall for the Safety population in the Randomized period. Spirometry data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal non clinically significant/abnormal clinically significant results. Data with and without bronchodilator at Screening will be summarized together with the spirometry data at Day 0 for the Safety population in the Pre-randomization period.

The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.2.30 | Full Lung Function Results Mean and 95% CI – Safety Population |
| TABLES | |
| 15.2.6.22 | Summary of Full Lung Function Results – Safety Population |
| LISTINGS | |

| TFL number | Title |
|---|---|
| 15.3.6.11 | Listing of Full Lung Function Data and Changes from Baseline |

### 12.6.4.4.5 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces, i.e. not centrally read. These data include the PR, QT, and QTcB intervals; QRS duration; and heart rate; and normality evaluation (normal, abnormal non-clinically significant, clinically significant, together with any PI comments to the abnormality). In addition the QTcF value will be presented.

ECG data values and normality evaluations will be listed by product and study day (Screening, Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit) together with changes from baseline and shift in normality. ECG data from subjects which had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for ECG data at baseline, and Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit by randomization arm. ECG data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.21 | Summary of ECG Results – Safety Population |
| LISTINGS | |
| 15.3.6.10 | Listing of ECG Data and Changes from Baseline |

### 12.6.4.4.6 Assessment of Cough

Cough questionnaire is assessed on a daily basis from Day 0 to Day 6 and Day 30 Visit, Day 60 Visit and Day 90 Visit. Questionnaire details are reported in Section **7.3.7** "**Cough Assessment**".

The number and percentage of subjects reporting a cough will be summarized by randomization arm and presented for the day prior to the assessment. The responses to the individual items, including the VAS evaluating the level of cough bother and 3 Likert scales mesuring the intensity, the frequency of cough and the amount of sputum production will be listed and summarized on each day by randomization arm, for all subjects who filled in the questionnaire. The answers to the open question related to any other important observation will be listed.

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The data will be presented in the below outputs:

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.6.25 | Summary of Cough Assessments Over Study – Safety Population |
| 15.2.6.25.1 | Summary of Cough Assessments by Study Day – Safety Population |
| LISTINGS | |
| 15.3.6.23 | Listing of Cough Assessment Results |

# 13    ANALYSIS AND REPORTING

## 13.1    Interim Analysis and Data Monitoring

No interim analysis is planned on this study.

A Clinical Research Associate ("Monitor") from ▇▇▇▇ will be responsible for the monitoring of the study. Monitoring will be performed according to ▇▇▇▇ standard operating procedures (SOPs) and as per the agreed monitoring plan with PMI.

The PI, or a designated member of the PI'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.

All changes to the source data will have to be approved by the PI.

## 13.2    Safety Reporting

Statistical summaries required for safety reporting will be made available to PMI medical safety officer following database lock. The TFLs are listed in the table below.

| TFL number | Title |
| --- | --- |
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP Set |
| 15.2.1.4.3.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PP Set |
| 15.2.1.4.3.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set |
| 15.2.6.1 | Summary of Adverse Events– Safety Population |
| 15.2.6.2 | Summary of Adverse Events by Product Use Category in Ambulatory – Safety Population |

| TFL number | Title |
| --- | --- |
| 15.2.6.3 | Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.4 | Summary of Adverse Events by Product Use Category, System Organ Class and Preferred Term – Safety Population |
| 15.2.6.5 | Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population |
| 15.2.6.6 | Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population |
| 15.2.6.7 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.8 | Summary of Adverse Events Leading to Study Discontinuation by Actual Exposure, System Organ Class and Preferred Term – Safety Population |
| 15.2.6.9 | Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.10 | Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.11 | Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.12 | Summary of Serious Adverse Events by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.15 | Summary of THS 2.2 Menthol Device Events – Safety Population |

## 13.3    Topline Results

Topline results, composed of key statistics and study results listings, will be made available to PMI management following database lock and prior to completion of the complete set of TFLs. The topline TFLs are listed in the table below.

| TFL number | Title |
| --- | --- |
| FIGURES | |
| 15.1.1.1 | Forest Plot of Statistical Analysis of Biomarkers of Exposure on Day 5 and Day 90 – PP Set |
| 15.1.1.2 | Biomarker of Exposure Geometric Mean and 95% CI – PP Set |
| TABLES | |
| 15.2.3.1.1 | Analysis of COHb, MHBMA, 3-HPMA, S-PMA, Total NNAL versus mCC on Day 5/90 Visit for THS 2.2 Menthol vs mCC for the Primary Objective – PP Set |
| 15.2.4.1.1 | Descriptive Statistics of Blood COHb (%) – PP Set |
| 15.2.4.2.1 | Descriptive Statistics of MHBMA in 24-hour Urine Collection – PP Set |
| 15.2.4.3.1 | Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – |

| TFL number | Title |
|---|---|
|  | PP Set |
| 15.2.4.4.1 | Descriptive Statistics of S-PMA in 24-hour Urine Collection – PP Set |
| 15.2.4.5.1 | Descriptive Statistics of Total NNAL in 24-hour Urine Collection – PP Set |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP Set |
| 15.2.1.4.3.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PP Set |
| 15.2.1.4.3.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set |

## 13.4     Final Analyses

Final analyses for this study will be performed only after database lock. A pre-analysis data review meeting will be held prior to database lock and completion of the final analyses. In addition, no database may be locked, randomization code unblinded, or analyses completed until the final version of this SAP has been approved.

Any post-hoc, additional exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as applicable. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

The list of all tables, figures and listings to be presented are included in the relevant sections of the SAP.

## 13.5     Clinical Trials.gov Reporting

Statistical summaries which will be evaluated for publishing on the Clinical trials.gov website are listed in the table below.

| TFL number | Title |
|---|---|
| TABLES |  |
| 15.2.3.1.1 | Analysis of COHb, MHBMA, 3-HPMA, S-PMA, Total NNAL versus mCC on Day 5/90 Visit for THS 2.2 Menthol vs mCC for the Primary Objective – PP Set |
| 15.2.6.3.1 | Summary of Adverse Events (Incidence >5% in any Study Arm) by System Organ Class and Preferred Term – Safety Population |
| 15.2.1.1 | Summary of Subject Disposition – All Screened Subjects |

## 14     DATA PRESENTATION

A separate TFL style guide document will be provided by PMI.

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# 16 APPENDICES

## 16.1 Study Assessments

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

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

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

| Study Day | Screening | Confinement Period | | | | | | | | | | Ambulatory Period | | | | | | Safety Follow-up [z] |
| | | | | | | | | | | | Day 30 Visit ± 5 days | | Day 60 Visit ± 5 days | | Day 60 Visit ± 5 days | | |
| | -30 to -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 [y] | 30 | 31 | 60 | 61 | 90 | 91 | 91 to 119 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Intention to quit smoking in the next 6 months (prochaska 'Stage of Change questionnaire) | ● | ● | | | | | | | | | ● | | ● | | ● | | |
| Readiness to comply with study protocol: to abstain from smoking for up to 91 days | ● | ● | | | | | | | | | | | | | | | |
| Identification of mCC | ● | ● | | | | | | | | | | | | | | | |
| THS 2.2 Menthol demonstration | ● | | | | | | | | | | | | | | | | |
| THS 2.2 Menthol product test and readiness to use the product [g] | | ● | | | | | | | | | | | | | | | |
| Question on product Preference | | ● | | | | | | | | | | | | | | | |
| Collection of mCC butts for accountability | | | ● | ● | ● | ● | ● | ● | ● | ● | | | | | | | |
| Collection tobacco plugs of used Menthol Tobacco Sticks for further analysis | | | | | ● | ● | ● | ● | ● | | ● | | ● | | ● | | |

| | Screening | Confinement Period | | | | | | | | | | Ambulatory Period | | | | | | Safety Follow-up [z] |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | | | | | | Day 30 Visit ± 5 days | | Day 60 Visit ± 5 days | | Day 60 Visit ± 5 days | | |
| **Study Day** | -30 to -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 [y] | 30 | 31 | 60 | 61 | 90 | 91 | 91 to 119 |
| Collection of empty/partially used Menthol Tobacco Stick for accountability | | | | | | | | | | | ● | | ● | | ● | | |
| CO breath test [h] | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | |
| B: BoExp in blood: COHb [i] | | | ● | ● | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | ● | |
| B: BoExp to nicotine in plasma: nicotine, cotinine [j] | | | | ● | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | |
| U: Ames Mutagenicity (see Table A2) | | | | ● | | | | | ● | | | | | | ● | | |
| U:all urinary BoExp (primary and secondary, and BoExp to nicotine) [j] (see Table A2) | | | ● | ● | ● | ● | ● | ● | ● | | | ● | | ● | | ● | | |
| U:all urinary BoExp in 4-hour fraction (primary and secondary, and BoExp to nicotine) (see Table A3) | | | ● | | | | | | | | | | | | | | ● | |
| B:Risk markers: hs-CRP, fibrinogen, homocysteine, LDL, HDL [k] | | | | ● | | | | | | | | | ● | | ● | ● | |
| B: Risk Marker: sICAM-1 [l] | | | | ● | | | | | | | ● | | ● | | ● | | ● | |

| | Screening | Confinement Period | | | | | | | | | Ambulatory Period | | | | | | Safety Follow-up [z] |
| | | | | | | | | | | | Day 30 Visit ± 5 days | | Day 60 Visit ± 5 days | | Day 60 Visit ± 5 days | | |
| **Study Day** | **-30 to -3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **5** | **6 [y]** | **30** | **31** | **60** | **61** | **90** | **91** | **91 to 119** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B: Risk Marker: HbA1c, Apo A1 ansd and Apo B [m] | | | | ● | | | | | | | | | | | | ● | |
| U: Risk markers I 24-hour urine: 8-epi- PGF2α and 11-DTX-B2 (see Table A2) [n] | | | | ● | | | | | ● | | ● | | ● | | ● | | |
| U: Risk markers I 4-hour urine: 8-epi- PGF2α and 11-DTX-B2 (see Table A3) | | | ● | | | | | | | | | | | | | ● | |
| One caffeine tablet (200 mg caffeine) | | | | ● | | | | | ● | | | | | | ● | | |
| B: CYP1A2 activity | | | | ● | | | | | ● | | | | | | ● | | |
| B: CYP2A6 activity | | | | ● | | | | | | ● | | | | | | ● | |
| B: Oxysterols | | | | ● | | | | | | ● | | | | | | ● | |
| Product use diary [o] | | | | | | | | | | ● | ● | ● | ● | ● | ● | ● | |
| QSU-brief questionnaire [p] | | | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | ● | | |
| MNWS (revised version) [q] | | | ● | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | ● | |
| MCEQ (modified version; THS 2.2 Menthol and mCC arms) [r] | | | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | ● | | |
| HST (THS 2.2 Menthol and mCC arms) [s] | | | | ● | ● | | | ● | | | ● | | ● | | ● | | |

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| | Screening | Confinement Period | | | | | | | | | Ambulatory Period | | | | | | Safety Follow-up z |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | | | | | | Day 30 Visit ± 5 days | | Day 60 Visit ± 5 days | | Day 60 Visit ± 5 days | | |
| Study Day | -30 to -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6[y] | 30 | 31 | 60 | 61 | 90 | 91 | 91 to 119 |
| HST questionnaire | | | | ● | | | | ● | | | ● | | ● | | ● | | |
| Assessment of cough [t] | | | | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | ● | |
| Risk Factor Surveillance System Questionnaire | | | ● | | | | | | ● | | | | | | | | |
| Smoking Questionnaire | | | ● | | | | | | ● | | | | | | | | |
| Supplemental questions [u] | | | ● | | | | | | ● | | | | | | | | |
| AE/SAE recording | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| B: Bio-banking for BoExp and risk markers [vw] | | | | ● | | | | | | ● | | | | | | ● | |
| U: Bio-banking for BoExp and risk markers [v] | | | | ● | | | | | | ● | | | | | ● | | |
| B: Bio-banking for transcriptomics [vw] | | | | ● | | | | | | ● | | | | | | ● | |
| Nasal Lavages | | | | ● | | | | | | | | | | | ● | | |
| Nasal Epithelial collection [v] | | | | ● | | | | | | ● | | | | | ● | | |
| Buccal Collection [v] | | | | ● | | | | | | ● | | | | | ● | | |

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

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

b: Including height (only at Screening). Weight will be evaluated also as risk marker on Day -2 Visit on D 90 Visit (Day 91).

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

d: Spirometry without bronchodilator will be performed at screening only and must be done prior to spirometry with bronchodilator.

Spirometry with bronchodilator will be done at Screening, Day 0, Day 6, and Day 90 Visit (Day 91). At screening, spirometry with bronchodilator will be done at least 1 hour after smoking. On Day 0, Day 6, and Day 90 Visit, spirometry with bronchodilator will be performed prior to product use (mCC or THS 2.2 Menthol). Spiromety using helium technique and spirometry using the single breath technique for CO will be performed Day 0, Day 6, and Day 90 Visit (Day 91) prior to product use.

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

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

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

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

i: COHb; Assessments should be done in conjunction with CO breath tests, where applicable.

Day -1 and from Day 1 to Day 4: one blood sample in the evening around 08:00 PM.

On Day 0, two blood samples will be collected: one blood sample will be collected prior to gas transfer assessment and prior to product use (the COHb levels measured will serve for adjustment of gas transfer values only), the second blood sample will be collected in the evening between 08:00 PM and 09:30 PM.

Day 5: one blood sample within 15 minutes prior to first product use (for subjects in THS 2.2 Menthol and mCC arms) and between 08:00 AM and 09:30 AM for subjects in the SA arm. The three other blood samplings will be conducted as described in Section 9 of the protocol.

On Day 6: one blood sample will be collected prior to the gas transfer assessment and prior to product use (the COHb levels measured will serve for adjustment of gas transfer values only).

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

On Day 90 Visit: one blood sample will be collected on Day 90, irrespective of the time of product use. One blood sampling will be collected on Day 91 prior to gas transfer assessment, and product use (the COHb levels measured will serve for adjustment of gas transfer values only).

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

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

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

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

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

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

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

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

o: Daily during ambulatory period only (from time of Discharge on Day 6 to time of discharge of Day 91). Use of any tobacco/nicotine containing products will be captured in the e-diary.

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

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

r: MCEQ: Day -1 to Day 5 on a daily basis, and on Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90) in Day -1 and Day 0 on all subjects, from Day 1 in THS 2.2 Menthol and mCC arms.

s: On Day 0, HST assessment will be done in all subjects smoking mCC compatible with the HST SODIM® device. On Day 1, Day 4, Day 30 Visit (Day 30) , and Day 60 Visit (Day 60) and Day 90 Visit (Day 90), HST will be done in all subjects in the THS 2.2 Menthol and mCC arms. On Day 1 and Day 4, full day HST recording will be done. On Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90), 4 hours of recording will be done. Smoking topography with the HST SODIM® device will not be done in subjects smoking mCC that are incompatible with the HST SODIM® device (e.g. slim mCC). No HST assessments will be done in subjects in the SA arm.

t: Cough questionnaire to be done daily from Day 0 to Day 6 prior product use but no later than 10: 00 AM and on Day 30 Visit (Day 31) Day 60 Visit (Day 61) and Day 90 visit (Day 91) no later than 10:00 AM, irrespective of product use.

u: Subjects will be assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by the means of 2 questionnaires. The questionnaires will be asked with the following sequence:

1-a standard questionnaire (Behavioral Risk Factor Surveillance System Questionnaire 2011) (CDC, 2011a) which is validated

2 a Smoking Questionnaire (SQ) to be validated. Immediately after the administration of the SQ, some supplemental questions will be collected on the completion of the SQ questionnaire. This supplemental question 1 is related to the time which the subject spends to complete the SQ and should be completed by site.

The Behavioral risk factor surveillance and the SQ are self-administrated to be answered by subjects. The supplemental questions will be asked by the site.

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

w: Has to be done in at least 10 hours of fasting condition.

x: Subject must not have eaten 30 minutes prior to the start of procedures.

y: All examinations listed at the Day of Discharge (Day 6) will be conducted in subjects whose participation in the study is prematurely terminated and for all subjects who have tried the product on admission

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

Table A2      Schedule for 24-hour Urine Collection Assessments

| | Baseline Period 24-hour urine | Confinement Exposure Period 24-hour urine | | | | | Ambulatory Exposure Period 24-hour-urine | | |
|---|---|---|---|---|---|---|---|---|---|
| | Day 0 to Day 1 | Day 1 to Day 2 | Day 2 to Day 3 | Day 3 to Day 4 | Day 4 to Day 5 | Day 5 to Day 6 | Day 30 to Day 31 | Day 60 to Day 61 | Day 90 to Day 91 |
| BoExp in urine [a] | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Creatinine | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| 11-DTX-B2, 8-epi-PGF2 α | ● | | | | | ● | ● | ● | ● |
| Ames test | ● | | | | | ● | | | ● |
| Bio-banking [b] | ● | | | | | ● | | | ● |

a: MHBMA, 3-HPMA, S-PMA, Total NNAL, 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ.

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

Abbreviations: 1-NA = 1-aminonaphthalene; 2-NA = 2-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; BoExp = biomarker(s) of exposure; CEMA = 2-cyanoethylmercapturic acid; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropyl-mercapturic acid; NEQ = nicotine equivalents; Total NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; total NNN = N-nitrosonornicotine; MHBMA = monohydroxybutenyl mercapturic acid; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid.

Table A3        Schedule for 4-hour Urine Collection Assessments

|  | Baseline Period 4-hour urine fraction | Ambulatory Period 4-hour urine fraction |
|---|---|---|
|  | Day -1 | Day 90 Visit (Day 91) |
| BoExp in urine [a] | ● | ● |
| Creatinine | ● | ● |
| 11-DTX-B2 and 8-epi-PGF2 $\alpha$ | ● | ● |

a: MHBMA, 3-HPMA, S-PMA, Total NNAL, 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ.

Abbreviations: 1-NA = 1-aminonaphthalene; 2-NA = 2-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; BoExp = biomarker(s) of exposure; CEMA = 2-cyanoethylmercapturic acid; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropyl-mercapturic acid; NEQ = nicotine equivalents; Total NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; total NNN = N-nitrosonornicotine; MHBMA = monohydroxybutenyl mercapturic acid; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid.