# STATISTICAL ANALYSIS PLAN

## A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile of the Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M) following single use in smoking, healthy subjects compared to menthol conventional cigarettes

Study Product: Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 Menthol)

Sponsor Reference No.: P2M-PK-04-JP

Sponsor:
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Study Site:
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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).

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# 3 INTRODUCTION

This SAP has been developed to supplement the statistical analyses described in the clinical study protocol version 2.0 dated 18 May 2015.

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 TFL shells 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**).
- The Committee for Medicinal Products for Human Use (CHMP) Guideline on the Investigation of Bioequivalence (**CHMP, 2010**).
- The Appendix IV of the CHMP Guideline on the Investigation on Bioequivalence (**CHMP Appendix IV, 2011**).
- Food and Drug Administration (FDA) Guidance to Industry for Statistical Approaches to Establishing Bioequivalence (**FDA, 2001**).
- Electronic case report forms (eCRF) Version 4.0 dated 04 May 2015.
- Biostatistical Addendum – Subject Randomization List version 2.0 (16 June 2015).

## 3.1 Revision History

| Version | Date of Revision | Revision |
|---|---|---|
| 1.0 | 17 November 2015 | Final 1 |

# 4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used within this SAP.

| | |
|---|---|
| $\%AUC_{extr}$ | Percentage of AUC that is extrapolated from $t_{last}$ to infinity |
| ADL | Activities of daily living |
| AE | Adverse event |
| ANOVA | Analysis of variance |
| ATC | Anatomical Therapeutic and Chemical |
| AUC | Area under the concentration-time curve |
| $AUC_{(0-\infty)}$ | Area under the concentration-time curve from $T_0$ extrapolated to infinity |
| $AUC_{(0-last)}$ | Area under the concentration-time curve from $T_0$ to time of last quantifiable concentration |
| $AUC_{(0-t')}$ | Partial AUC, where t' is the subject-specific time of maximum nicotine concentration following the single use of cigarettes or nicotine nasal spray |
| BLQ | Below the Lower limit of Quantification |
| BMI | Body mass index |
| CC | Conventional cigarette(s) |
| CD | Compact disc |
| CI | Confidence interval |
| $C_{last}$ | Last quantifiable concentration |
| $C_{max}$ | Maximum concentration |
| CC | Conventional Cigarette |
| CH | Cigarette Holder |
| CHTP | Carbon Heated Tobacco Product |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{last}$ | The last quantifiable concentration |
| $C_{max}$ | Maximum observed plasma concentration. |
| CO | Carbon monoxide |
| COHb | Carboxyhemoglobin |
| COT | Cotinine |
| CRF | Case report form |
| CRO | Contract research organization |
| CSR | Clinical study report |
| CTCAE | Common terminology criteria for adverse events and common toxicity criteria |
| CTMS | Clinical trial management system |
| CV | Coefficient of variation |
| CYP2A6 | Cytochrome P450 2A6 |

| | |
|---|---|
| DDE | Drug Dictionary Enhanced |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EOS | End of study |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FTND | Fagerström test for nicotine dependence (revised version) |
| FVC | Forced vital capacity |
| GCP | Good Clinical Practice |
| HCOT | Trans-3'hydroxycotine |
| HIV | Human immunodeficiency virus |
| HPHCs | Harmful and potentially harmful constituents |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IP | Investigational product |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| IV | Intravenous |
| IxRS | Interactive web/voice response system |
| LLN | Lower limit of the normal range |
| LLOQ | Lower limit of quantification |
| LS | Least Squares |
| mCC | Menthol conventional cigarette |
| MCEQ | Modified cigarette evaluation questionnaire |
| MedDRA | Medical dictionary for regulatory activities |
| MRTP | Modified risk tobacco product |
| MSE | Mean square error of the fitted model residual |
| NR | No Result |
| PK | Pharmacokinetic(s) |
| PMI | Philip Morris International |
| PT | Preferred Term |
| QC | Quality control |
| QSU-brief | Questionnaire of smoking urges |
| QTcB | QT Interval Corrected using Bazett's Formula |
| QTcF | QT Interval Corrected using Fridericia's Formula |
| REML | Restricted Maximum Likelihood |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard Deviation |
| SHM | Sample handling manual |
| SOC | System Organ Class |
| SOP | Standard operating procedure |
| T | Time point |

| | |
|---|---|
| t’ | Subject-specific time of maximum nicotine concentration following single use of mCC or CHTP 1.1 M product |
| $T_0$ | Time point of first product use during study day |
| $t_{½}$ | Half-life |
| $t_{last}$ | Time of last quantifiable concentration |
| $t_{max}$ | Time to maximum concentration |
| TFL | Tables, Figures, and Listings |
| UBC | United BioSource Corporation |
| ULN | Upper limit of the normal range |
| ULOQ | Upper limit of quantification |
| VAS | Visual analogue scale |
| WBC | White blood cell (count) |
| WHO | World Health Organization |
| $\lambda_z$ | Terminal elimination rate constant |

The following special terms are used in this SAP:

| | |
|---|---|
| End of Study | date when the subject completes his/her 7-day safety follow-up period |
| First product use time point | Start of the product test use. |
| mCC | The term ‘menthol conventional cigarette’ refers to manufactured and commercially available menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products. |
| Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M) | CHTP 1.1 M is a tobacco stick which is comparable in shape and form, and is used in a similar manner to a menthol conventional cigarette. To use the CHTP 1.1 M, the consumer removes the protective cap and uses a conventional lighting method to ignite the heat source. [redacted], the aerosol generated by the heating process is inhaled by placing the lips on the filter and drawing air through the CHTP 1.1 M. |
| Randomization | Assignment to the respective product at any time on Day -1 utilizing an interactive web and voice response system (IxRS). On Day 1, the subjects will be individually informed about the product they are randomized to just before the first product use. |
| Screen failure | Subject who signs informed consent form but does not meet |

the entry criteria prior to enrolment at Admission (Day -3) or met all entry criteria, but was not enrolled due to completion of enrolment (*i.e.,* supernumerary subject). Re-screening of subjects who did not meet any entry criteria will not be permitted.

# 5 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Primary Objective and Endpoints

1. To evaluate the rate and amount of nicotine absorbed (as assessed by maximum plasma concentration [$C_{max}$] and area under the concentration-time curve [AUC] from start of product use to time of last quantifiable concentration [$AUC_{(0\text{-last})}$]) from the CHTP 1.1 M relative to mCC following single use of the CHTP 1.1 M and mCC.

   Endpoints:

   - $C_{max}$
   - $AUC_{(0\text{-last})}$

## 5.2 Secondary Objectives and Endpoints

1. To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to infinity [$AUC_{(0\text{-}\infty)}$], up to 12 hours [$AUC_{(0\text{-}12)}$], and partial $AUC_{(0\text{-}t')}$, where t' is the subject-specific time of maximum nicotine concentration following single use of the mCC [$AUC_{(0\text{-}t')}$]) between the CHTP 1.1 M and mCC.

   Endpoints:

   - $AUC_{(0\text{-}\infty)}$
   - $AUC_{(0\text{-}12)}$
   - Partial $AUC_{(0\text{-}t')}$

2. To evaluate the time to the maximum concentration ($t_{max}$) of nicotine for the CHTP 1.1 M as compared to mCC.

   Endpoint:

   - $t_{max}$

3. To describe the terminal half-life ($t_{1/2}$) of plasma nicotine for the CHTP 1.1 M and mCC.

   Endpoint:

   - $t_{1/2}$

4. To describe the differences on urge-to-smoke over time between the CHTP 1.1 M and mCC.

   Endpoint:

   - Urge-to-smoke questionnaire (questionnaire of smoking urges brief [QSU-brief]) total score, factor 1 and factor 2

5. To describe product evaluation of the CHTP 1.1 M and mCC.

   Endpoint:

- Product evaluation questionnaire (modified cigarette evaluation questionnaire [MCEQ]) subscales scores

6. To describe the levels of carbon monoxide (CO) exposure for the CHTP 1.1 M as compared to mCC.
   Endpoint:
   - CO exposure biomarkers: levels of exhaled CO and carboxyhemoglobin (COHb) in blood

7. To monitor the safety during the study.
   Endpoints:
   - Incidence of adverse events (AEs)/serious adverse events (SAEs)
   - Respiratory symptoms: cough assessment by visual analogue and Likert scales and one open question
   - Vital signs
   - Spirometry
   - Electrocardiogram (ECG)
   - Clinical chemistry, hematology, and urine analysis safety panel
   - Physical examination
   - Concomitant medication.
   - Incidence of CHTP 1.1 M malfunctions and misuse; [redacted]

## 5.3 Additional Endpoints

The following additional assessments (for baseline characteristics) will be made:

- Serology for human immunodeficiency virus 1/2 and hepatitis B and C
- Urine pregnancy test (female subjects of childbearing potential only), urine cotinine test, urine drug screen
- Alcohol breath test
- Chest X-ray
- Nicotine dependence to be assessed with the Fagerström test for nicotine dependence revised version
- Cytochrome P450 2A6 (CYP2A6) activity expressed as *trans*-3'-hydroxycotinine/cotinine molar metabolite ratio in plasma

## 5.4 Study Hypotheses And Evaluation Criteria

### 5.4.1 Hypotheses

Given that the objective of this study is to determine the point estimate and precision of the ratio of the CHTP 1.1 M:mCC for $C_{max}$ and $AUC_{0\text{-last}}$, there is no statistical hypothesis to be tested.

### 5.4.2 Evaluation Criteria

The study will target to describe the 95% confidence intervals (CI) of the CHTP 1.1 M:mCC ratio for the primary nicotine PK parameters estimated with a precision of ±30%.

# 6 INVESTIGATIONAL PLAN

## 6.1 Study Design

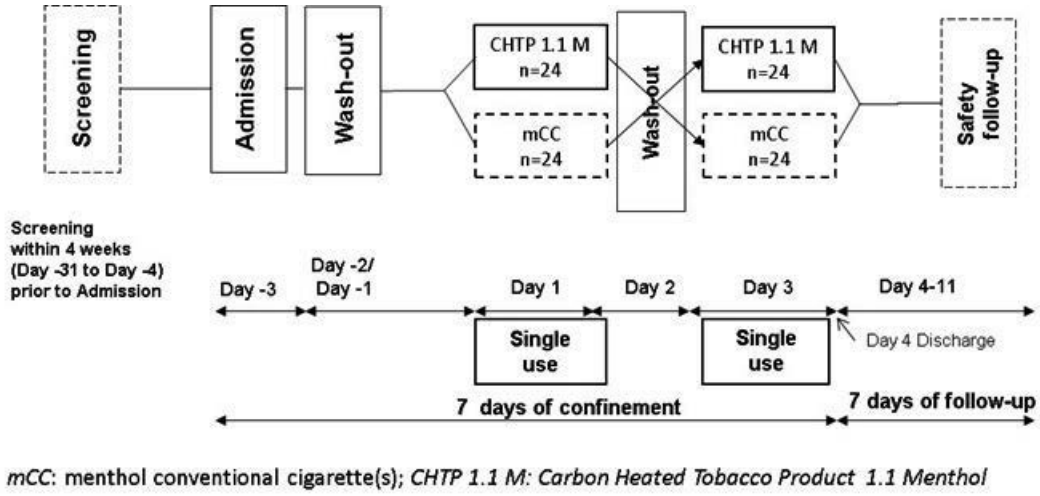
This is a randomized, controlled, 2-period, 2-sequence, single-use crossover study. Each subject will receive CHTP 1.1 M and mCC (Figure 1 Study Flow Chart).

The end of the study is defined as the date when the last subject completes his/her 7-day safety follow-up period.

Subjects that terminate the study after Enrolment and prior to completion of the study will be asked to undertake early termination procedures.

**1) Screening and Admission (from the ICF Signature to the Enrolment at Admission):**

A Screening Visit will be conducted within 4 weeks (Day -31 to Day -4) prior to Admission to the investigational site (Day -3). A demonstration of the CHTP 1.1 M will be done by the site collaborators during the Screening Visit. Screening procedures do not necessarily have to be conducted on the same day. On Day -3 (Admission), after all inclusion/exclusion criteria are checked, all eligible subjects will be enrolled and perform a product test using 3 to 5 CHTPs 1.1 M. After product test, subjects not ready to use the CHTP 1.1 M will be discontinued. All subjects that are not enrolled are considered as screen failures. Subject will be instructed not to smoke in the morning prior to Admission. After Admission, smoking will not be allowed until blood drawing for the assessment of CYP2A6 activity and spirometry have been performed (Section 9.2). After these assessment procedures, smoking will be allowed until 11.00 PM at Admission.




*mCC*: menthol conventional cigarette(s); *CHTP 1.1 M: Carbon Heated Tobacco Product 1.1 Menthol*

**Figure 1 Study Flow Chart**

### 2) The Investigational Period (from Day -2 to Discharge):

The Investigational period will consist of 2 periods (Period 1, Period 2) with each period consisting of approximately 48 to 57 hours smoking abstinence and 1 day of single product use.

Period 1: From Day -2 to Day 1. After Day 1 product use, the subject will start his/her washout for period 2

Period 2: From Day 2 to Day 3. The products should be used at the same time (within 1 hour) on Day 1 and Day 3

48 eligible, healthy smoking subjects will be randomized to one of 2 sequences:

**Table 1 Definition of Randomization Sequences**

| Sequence | Sample Size |
|---|---|
| 1. CHTP 1.1 M then mCC | 24 |
| 2. mCC then CHTP 1.1 M | 24 |

Each sex and smoking strata (International Organization for Standardization [ISO] nicotine levels ≤ 0.6 mg vs. >0.6 to 1.0 mg) will have a quota applied to ensure they represent at least 40% of the study population for each Sequence (Sequence 1 and Sequence 2).

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

Subjects will be discharged from the investigational site in the morning of Day 4 after performance of Discharge assessments.

**3) The Safety Follow-up Period (from Discharge until Day 11):**

A 7-day safety follow-up will be done for the recording of spontaneously reported AEs and SAEs (passive surveillance) and the active follow-up by the investigational site of AEs/SAEs ongoing at Discharge. Any AE will in general be followed-up until resolved, stabilized (*i.e.*, no worsening of the event), or until a plausible explanation for the event has been found.

The end of study for the subject is defined as the date of completion or discontinuation on Subject status form completed. AEs/SAEs not resolved or not stabilized at EOS are to be recorded as ongoing at EOS.

## 6.2 Selection of Study Population

### 6.2.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria can be enrolled into the study:

1. Subject has signed the ICF and is able to understand the information provided in the ICF.
2. Subject is at a minimum 23 years of age (inclusive) at Screening.
3. Subject is Japanese.
4. Currently smoking, healthy subject as judged by the Investigator or designee based on assessments from the Screening period (*e.g.*, safety laboratory, spirometry, vital signs, physical examination, ECG, and medical history, X-ray).
5. Subject smokes at least 10 commercially available mCCs per day for the last 4 weeks prior to Screening and Admission, based on self-reporting (no brand restriction). Furthermore, the subject has been smoking for at least the last 3 consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).
6. The subject does not plan to quit smoking in the next 3 months.
7. The subject is ready to accept interruptions of smoking for up to 6 days.
8. The subject is ready to accept using the CTHP 1.1 M.

### 6.2.2 Exclusion Criteria

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

1. As per the Investigator's 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, or physically or mentally incapable of giving consent (*e.g.*, emergency situation, under guardianship, subject in a social or sanitary establishment, prisoners, or subjects who are involuntarily incarcerated).
3. The subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator or designee would jeopardize the safety of the subject.
4. The subject has ($FEV_1$/FVC) < 0.7 and $FEV_1$ < 80% predicted value at post-bronchodilator spirometry.
5. The subject has asthma condition ($FEV_1$/FVC < 0.75 and reversibility in $FEV_1$ > 12% (or > 200 mL) from pre- to post-bronchodilator values).
6. The subject has a body mass index (BMI) < 18.5 or ≥ 32.0 kg/$m^2$.
7. As per the Investigator's 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.
8. The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or nicotine replacement therapies), as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
9. The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer) which has an impact on CYP2A6 activity.
10. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in study.
11. The subject has a positive urine drug test.
12. The subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.
13. Donation or receipt of whole blood or blood products within 3 months prior to Admission.
14. The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
15. The subject is an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, child).
16. The subject has participated in a clinical study within 3 months prior to the Screening Visit.
17. The subject has been previously screened in this study and failed to meet the eligibility criteria.
18. For women of childbearing potential only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission if not post-menopausal) or is breast feeding.

19. For women of childbearing potential only: Subject does not agree to use an acceptable method of effective contraception: intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the safety follow-up period. Hormonal contraception with estrogen containing products is NOT allowed in this study.

## 6.3 Product Allocation and Blinding

### 6.3.1 Methods of Assigning Subjects to Treatment Sequences

Randomization to product exposure sequence will be done through [redacted].

Each sex and each of the smoking level (ISO nicotine levels ≤0.6 mg and >0.6 to 1 mg) will have a quota applied to ensure they represent at least 40% of the total study.

In particular, the maximum number of subjects having the same sex or nicotine level value will be limited to 28.

The randomization of the planned sample size of 48 subjects will be ensured by applying quota to the number of subjects per each sequence (24 subjects).

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

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

### 6.3.2 Blinding

This is an open-label study; therefore the subjects and Investigators or designee will be unblinded to the subject's sequence. However, there will be a limited degree of blinding in the data review and data analysis process. In particular, PMI and CRO personnel will be blinded to the randomized sequence as summarized in Table 2:

**Table 2 Description of Blinded Study Personnel**

| Blinded Study Personnel | End of Blinding Period |
|---|---|
| PMI and CRO study statisticians | After the SAP finalization or database lock[1], whichever comes last |
| PMI clinical scientist | After the finalization of PMI blind database review[2]. Can be actively un-blinded when appropriate. |

1 Data will be accessible blinded to randomization sequence and to product use by means of a dummy randomization or masking.

2 As part of the PMI quality control (QC) activity, data listings will be reviewed by the CRO and PMI before database lock, with no access to the randomization information. Full details will be available in the data review plan.

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

### 6.3.3 Compliance to Product Allocation

Compliance for all sequences will be ensured by strict distribution of the products (product by product) and collection of used CHTP 1.1 M and the mCC butts after use will be documented in appropriate logs.

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

# 7 DERIVED AND COMPUTED VARIABLES

Mean change from baseline is the mean of all individual subjects' change from baseline values (baseline is defined in Section 11.1.4 "Definitions for Statistical Data Analysis"). 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.

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

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

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

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

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

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

The geometric coefficient of variation (CV) will be calculated using the following formula:

$$CV = 100\sqrt{e^{\text{var}} - 1}$$

where var = the variance from the log transformed data.

## 7.1 Pharmacokinetic Parameters

The following PK parameters will be determined from the plasma concentration-time profiles of nicotine using non-compartmental procedures in WinNonlin Phoenix, Version 6.2, or higher:

**Table 3: Definition of PK Parameters**

| Parameter | Definition |
|---|---|
| $AUC_{(0\text{-last})}$ | Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration. |
| $AUC_{(0\text{-t'})}$ | Area under the plasma concentration-time curve from start of product use to the subject-specific time (t') of maximum nicotine concentration following single use of mCC or CHTP 1.1 M product. |
| $AUC_{(0\text{-}12)}$ | Area under the plasma concentration-time curve from start of product use to the 12 hours time point. |
| $AUC_{(0\text{-}\infty)}$ | Area under the plasma concentration-time curve from start of product use extrapolated to infinite time. |
| $\%AUC_{extrap}$ | Percentage of AUC that is extrapolated from $t_{last}$ to infinity. |
| $C_{max}$ | Maximum observed plasma concentration. |
| $C_{last}$ | Last quantifiable concentration. |
| $t_{last}$ | Time of the last quantifiable concentration. |
| $t_{max}$ | Time of maximum observed plasma concentration. |
| $\lambda_z$ | Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data. |
| $t_{1/2}$ | Terminal elimination half-life. |

Additional PK parameters may be determined in order to support the interpretation where appropriate.

The actual blood sampling times post-exposure collected in the eCRF will be used in the computation of the PK parameters, with the exception of pre-exposure (-15 mins) blood sampling time which will be considered as time zero ($T_0$).

### 7.1.1 Calculation of $C_{max}$ and $t_{max}$

The minimum requirement for the determination of the $C_{max}$ is the inclusion of at least one quantifiable concentration within 1 hour post-exposure.

$C_{max}$ and $t_{max}$ will be obtained directly from the plasma concentration-time profiles. If $C_{max}$ occurs at more than one time point, $t_{max}$ will be assigned to the first occurrence of the $C_{max}$.

### 7.1.2 Calculation of AUC

The minimum requirement for the calculation of the AUC is the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following $C_{max}$.

$AUC_{(0\text{-last})}$, $AUC_{(0\text{-}12)}$ and $AUC_{(0\text{-t'})}$ will be calculated using the linear trapezoidal method.

$AUC_{(0\text{-t'})}$ will be calculated by linear interpolation within WinNonlin, where t' is the subject-specific actual time of maximum nicotine concentration following single use of mCC or CHTP 1.1 M.

$AUC_{(0-\infty)}$ will be calculated as follows:

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

Where $C_{last}$ is the last quantifiable concentration and $\lambda_z$ is the terminal elimination rate constant.

$\%AUC_{extrap}$, the percentage of $AUC_{(0-\infty)}$ extrapolated beyond $t_{last}$, will be calculated according to the following formula:

$$\%AUC_{extrap} = \left( 1 - \frac{AUC_{0-last}}{AUC_{0-\infty}} \right) \text{x } 100$$

$AUC_{(0-\infty)}$ values where the percentage extrapolation is greater than 20% will be flagged in the data listings and will be reviewed for inclusion in the analysis during the pre-analysis data review.

### 7.1.3 Criteria for Calculating the Apparent Terminal Elimination Half-Life

$t_{1/2}$ will be calculated according to the following formula:

$$t_{1/2} = \frac{\ln(2)}{\lambda_z}$$

where $\lambda_z$ will be calculated by least squares (LS) linear regression of the terminal portion of the log-transformed plasma concentration-time curve.

The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. The concentrations included in the terminal elimination phase will be flagged in the data listings.

Period of Estimation

- Apparent terminal (elimination) half-lives will be calculated, where possible, over at least 2 half-lives. Where an apparent terminal half-life is estimated over less than 2 half-lives, it will be flagged in the data listings.
- An apparent terminal half-life will not be reported if it can only be calculated over a period that is less than 1.5 half-lives.

Number of Data Points

- At least 3 data points with nicotine concentration greater than the LLOQ will be used for each subject in the regression analysis. An apparent terminal half-life will not be reported if derived from less than 3 data points.

Goodness of Fit

- When assessing apparent terminal phases, the coefficient of determination, $R^2$ adjusted value, will be used as a measure of the goodness of fit of the data points to the determined line. This parameter will be used as it is considered to be a better assessment of the goodness of fit, compared to $R^2$, as it adjusts for the number of points included in the line therefore allowing for a more direct comparison between elimination phases determined using different numbers of data points.
- Apparent terminal half-life will only be calculated if the $R^2$ adjusted value of the regression line is greater than or equal to 0.7.

### 7.1.4 Anomalous Values

If a concentration value is considered to be anomalous due to being inconsistent with the expected PK profile it will be flagged in the listings and will be reviewed for inclusion in the analysis during the pre-analysis data review.

## 7.2 Biomarkers

### 7.2.1 Biomarkers of exposure

COHb measured in blood and exhaled CO will be investigated as a measure of exposure to CO. The CO breath test should be conducted in timely conjunction with the blood sampling for COHb where applicable.

### 7.2.2 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**):

$$CYP2A6 = \frac{HCOT[ng/mL] \times 5.202}{COT[ng/mL] \times 5.675}.$$

Any values below the LLOQ or above the upper limit of quantification (ULOQ) in the component parameters will not be imputed and the derived variable will be set to missing.

The conversion factor will be applied as follows:

| | |
|---|---|
| Cotinine (COT) | The molecular weight is 176.2178 g/mol (**Chemical Information Specialized Information Services RN:486-56-6**) Therefore to |

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

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

## 7.3 Questionnaires

### 7.3.1 Fagerström Test for Nicotine Dependence

Potential nicotine dependence will be assessed at Screening using the FTND in its revised version (**Heatherton et al, 1991)** as updated in 2012 (**Fagerström et al, 2012**) . These questions are to be answered by the subject themselves. It is conducted at Screening only to determine subject's 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<br>▪ 6 to 30 minutes<br>▪ 31 to 60 minutes<br>▪ After 60 minutes | 3<br>2<br>1<br>0 |
| 2 | Do you find it difficult to refrain from smoking in places where it is forbidden? | ▪ Yes<br>▪ No | 1<br>0 |
| 3 | Which cigarette would you hate most to give up? | ▪ The first one in the morning<br>▪ Any other | 1<br>0 |
| 4 | How many cigarettes per day do you typically smoke? | ▪ 10 or less<br>▪ 11 to 20<br>▪ 21 to 30<br>▪ 31 or more | 0<br>1<br>2<br>3 |
| 5 | Do you smoke more frequently during the first hours after waking than during the rest of the day? | ▪ Yes<br>▪ No | 1<br>0 |
| 6 | Do you smoke if you are so ill that you are in bed most of the day? | ▪ Yes<br>▪ No | 1<br>0 |

### 7.3.2 Questionnaire of Smoking Urges Brief

The QSU-brief (**Cox et al, 2001**) is a self-reported questionnaire completed by the subject himself/herself at single use study days in all subjects.

For subject on CHTP 1.1 M or on mCC: first assessment within 15 min prior to $T_0$, 9 assessments thereafter in relation to $T_0$: 15 min, 30 min, 45 min, 60 min, 2 hr, 4 hrs, 6 hrs, 9 hrs, and 12 hrs after $T_0$.

The QSU-brief consists of 10 items to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree) as presented in Table 5. Higher scores in this questionnaire indicate a higher urge-to-smoke.

**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 |

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 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.

### 7.3.3 Modified Cigarette Evaluation Questionnaire

The MCEQ (**Cappelleri et al, 2007**)will be completed by all randomized subjects on Day 1 and Day 3 to assess the degree to which subjects experience the reinforcing effects of smoking.

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.

### 7.3.4 Cough Assessment

Subjects will be asked if they have experienced a regular need to cough (e.g., coughing several times) in the last 24 hours prior to assessment. If the answer is 'yes', they will be asked to complete a visual analogue scale (VAS), three Likert scale questions and an open question assessing their cough during previous 24 hours. Assessments will be done on a daily basis on Day -2 and from Day 1 to Day 4. On Day 2 and Day 4, questionnaire must be asked 24 hours after $T_0$ of Day 1 and 24 hours after $T_0$ of Day 3.

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.

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 7.

**Table 7: 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. |

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

## 7.4 Categorical Variables

**Table 8: Categorical Variable Definitions**

| Variable | Categories | |
|---|---|---|
| BMI (kg/m$^2$) | Underweight: | < 18.5[1] |
| | 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 |
| ISO nicotine level (mg) | ≤ 0.6 | |
| | > 0.6 to ≤ 1.0 | |
| | > 1.0[1] | |
| ISO tar yields (mg) | 1-5 | |
| | 6-8 | |
| | 9-10 | |
| | >10[1] | |
| Daily mCC consumption (cig/day) | <10[1] | |
| | 10-19 | |
| | >19 | |

## Table 8: Categorical Variable Definitions

| Variable | Categories |
|---|---|
| CO breath test level (ppm) | ≤ 10<br>> 10 |
| COHb level | ≤ 2%<br>> 2% |
| Reason for discontinuation | Adverse events<br>Protocol violation<br>Withdrawal by subject<br>Subject lost to follow-up<br>Pregnancy<br>Sponsor's decision<br>Investigator's decision<br>Non-compliance with the assigned product<br>Non-compliance to the study procedures<br>Other |
| Reason for discontinuation (Safety Follow-up) | Adverse events<br>Protocol violation<br>Withdrawal by subject<br>Subject lost to follow-up<br>Pregnancy<br>Sponsor's decision<br>Investigator's decision<br>Non-compliance with the assigned product<br>Non-compliance to the study procedures<br>Other |
| Adverse event severity | Mild<br>Moderate<br>Severe |
| Adverse event relationship | Related<br>Not related |
| Adverse event expectedness | Expected<br>Unexpected |
| Action taken due to adverse event | Discontinuation from study<br>Related to product use (if any of the following applies: interrupted, stopped, or reduced)<br>Treatment given (yes/no)<br>Other action taken |

**Table 8: Categorical Variable Definitions**

| Variable | Categories |
|---|---|
| Outcome of adverse event | Fatal |
| | Not recovered or not resolved |
| | Recovered or resolved |
| | Recovered or resolved with sequelae |
| | Recovering or resolving |
| | Unknown |
| Seriousness Criteria | Fatal |
| | Life-threatening |
| | Requires / prolongation of hospitalization |
| | Results in disability/incapacity |
| | Congenital anomaly/birth defect |

[1] Note that due to inclusion criteria for the study there should not be any subjects underweight, or reporting <10 cig/day, or with ISO nicotine level > 1.0 mg; therefore these categories will not be presented unless there is at least one response.

# 8 SAMPLE SIZE JUSTIFICATION

A total of 48 subjects will be randomized.

The estimates for the within-subject CV for nicotine $C_{max}$ (60%) and $AUC_{(0\text{-last})}$ (50%) are based on the data collected in the ZRHM-PK-05 clinical study (Bethesda, 2013) comparing the nicotine PK profiles of THS 2.2 M, another MRTP candidate, and mCC in a Japanese population.

The sample sizes of this study assume a 5% drop-out rate.

Sample size calculations were conducted using SAS® version 9.2 for the 95% CI of the mean differences between paired observations (proc power onesamplemeans) in the natural log scale (**Senn, 2002**). The SAS® implementation of the method published by (**Beal, 1989)** was adopted to estimate the probability of obtaining at most the target 95% CI of ±30%.

A total of 48 subjects are needed to estimate the mean $C_{max}$ parameter ratio between CHTP 1.1 M and mCC with a 80% probability of obtaining a margin of error (95% CI) of at most ±30%, assuming that CHTP 1.1 M has a nicotine $C_{max}$ similar to mCC (ratio equal to 1.00). This sample size is sufficient to provide 80% probability of obtaining a margin of error of at most ±30% for the $AUC_{(0\text{-last})}$ ratio between CHTP 1.1 M and mCC, assuming a similar extent of nicotine absorption for the 2 products (ratio equal to 1.00).

# 9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

The analyses of Adverse Events will be performed by sequence; and by sequence and period if there are more than 10 AEs. The other safety evaluations will also analyzed by sequence and study day.

Shift tables for safety endpoints will not be produced for this study, because the relevant information will be provided in listings.

Statistical analysis for blood COHb (%) and exhaled CO (ppm) measurements and the QSU-brief questionnaire data will be performed including interaction terms for product and time point to enable LS means to be calculated at each time point in order to explore the pattern of the CHTP 1.1 M effect over time. The main comparison between products will be the comparison over all time points.

Serology for human immunodeficiency virus (HIV) 1/2 cannot be transferred because of privacy laws, therefore this endpoint is not presented in listings.

In addition to the PK parameters mentioned in the protocol, $\%AUC_{extrap}$ will be listed, as this parameter contains important information on the quality of the $AUC_{(0-\infty)}$.

# 10 ANALYSIS POPULATIONS

For analysis purposes, actual product exposure during single use days will be defined as:

- CHTP 1.1 Menthol: if there is a non-missing time for “Time of First Puff” (from CHTP 1.1 Menthol consumption page in eCRF), and no other product exposure definition is applicable.
- mCC: if there is a non-missing “Time of lighting the mCC” (from mCC product consumption eCRF page), and no other product exposure definition is applicable.

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

## 10.1 Screened Population

The screened population consists of all the subjects who give informed consent.

## 10.2 Randomized Population

The randomized population consists of all the subjects who were randomized on Day -1.

## 10.3 PK Population

The PK population consists of all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations that impact evaluability of the data (see Section 10.5 “Protocol Deviations”) will be included in the PK analysis sets.

## 10.4 Safety Population

The safety population consists of all the subjects who give Informed Consent and have at least one exposure to CHTP 1.1 M (including the product test at Admission).

## 10.5 Protocol Deviations

Protocol deviations are defined as those deviations from any procedure as 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, use of any nicotine tobacco-containing product during wash-out days, assessments not performed or performed outside the scheduled time windows, or use of oestrogen or other drugs that are known to affect CYP2A6 activity.

All protocol deviations will be entered into the clinical trial management system (CTMS) or other approved format.

Information from the source documents will represent the primary source of protocol deviations. Information following site monitoring and other manual reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in the CTMS or other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, documented and tracked as protocol deviations, as necessary.

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

### 10.5.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (at a population level) to determine whether they will be excluded from any of the analysis populations. 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 9.

**Table 9: Definition of Major Protocol Deviations**

| Category | Description |
|---|---|
| Violation | Violation of inclusion/exclusion criteria |
| Mis-randomization | Being administered the wrong product according to the randomization schedule |
| Mis-use of product | Use of any nicotine or tobacco–containing product other than the assigned product during the exposure period, or use of any nicotine tobacco-containing product during wash-out days (e.g. see Section 11.4 “Measurements of Product Compliance”). |
| Concomitant medication | Use of any drugs which are known to affect CYP2A6 activity |

Among the above criteria, violations of inclusion criteria 3, 6 to 8, or of the exclusion criteria 1, 3 to 16, and 19 will be assessed for their impact on the PK population and evaluated during the pre-analysis data review meeting (Section 6.3.1 “Methods of Assigning Subjects to Treatment Sequences”).

### 10.5.2 Minor Protocol Deviations

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

**Table 10: Definition of Protocol Deviation Categories**

| Category | Description |
|---|---|
| Time deviation (Plasma nicotine PK sample) | Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 11) |
| Time deviation (other assessment) | Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 11) |
| Assessment missing (Plasma nicotine PK sample) | Assessment is missing |
| Assessment missing (other assessment) | Assessment is missing |

10.5.2.1 Assessment Windows

On Day 1 and Day 3, subjects will use the product they are randomized to only once in the morning between 6:00 AM and 9:00 AM, and will abstain from the product or other nicotine/tobacco-containing items for the rest of the day. The start of the first product use must be in the window of 6:00 AM to 9:00 AM and should be at the same time (within 1 hour) for both days. The windows reported in Table 11 will be applied to the timing of data collection.

**Table 11: Definition of Assessment Windows**

| Assessment | Nominal Time point(s) (relative to $T_0$) | Window |
|---|---|---|
| Plasma nicotine PK sample (CHTP 1.1 M or mCC) | First sample<br>2, 4, 6, 8 and 10 min<br>15, 30 and 45 min<br>60 min<br>2, 4, 6, 9, 12 and 24 h | Within 15 min prior to $T_0$<br>+ 1 min<br>+ 2 min<br>+ 3 min<br>+ 5 min |
| Assessment of cough | Day -2<br>First assessment<br>24 h after $T_0$ | 06:30AM – 09:00AM<br>Prior to product use (Day 1 and Day 3)<br>24 hours (- 30 minutes) after $T_0$ of Day 1 and Day3 |
| QSU-brief (CHTP 1.1 M or mCC) | First time<br>15 min, 30 min, 45 min, 1 h and 2 h<br>4, 6, 9 and 12 h | Within 15 min prior to $T_0$<br>+10 min<br>+10 min |
| COHb blood sampling | First sample<br>15 min<br>60 min<br>4 and 12 h | Within 15 min prior to $T_0$<br>+ 2 min<br>+ 3 min<br>+ 5 min |
| CO breath test | First measurement<br>Second measurement<br>Third measurement<br>Fourth measurement | Within 15 min prior to $T_0$<br>12:00-01:30 PM<br>04:00-05:30 PM<br>08:00-09:30 PM |
| CYP2A6 | COT and HCOT measurements | Prior to smoking |

# 11 PLANNED STATISTICAL METHODS

## 11.1 General Considerations

Data analysis will be performed using SAS® Version 9.2 or higher.

Data listings will be provided for all data collected, ordered by sequence and subject, 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.

Safety data will be summarized for the safety population, PK data will be summarized and analyzed for the PK population, biomarker data will be summarized and analyzed for the PK population unless otherwise stated.

### 11.1.1 Stratified Presentation

Data summaries will be produced by sequence or product, sex (male and female), mCC nicotine level at Admission (ISO nicotine level ≤0.6 mg and >0.6 to ≤ 1mg), and time point (if applicable), unless otherwise stated.

Stratified presentations will be conducted on the PK populations for the following endpoints:

- Demographics
- Nicotine concentrations in blood
- PK parameters, during single use day
- COHb and CO values, during single use day
- MCEQ and QSU-brief questionnaires, during single use day

### 11.1.2 Subgroup Analyses

Exploratory subgroup analyses will be conducted for the primary endpoints in the following planned subgroups: sex (male or female), mCC nicotine level at Admission (ISO nicotine level ≤0.6 mg and >0.6 to ≤ 1mg) provided there are greater than 4 subjects in each category.

### 11.1.3 Descriptive Statistics

Descriptive statistics for continuous variables (number of subjects [n], number and percent of subjects with missing data, mean, standard deviation, median, first and third quartiles, minimum and maximum) and categorical data (n, number and percent of subjects with missing data, by category) will presented by product exposure and overall. Summaries will be presented at Baseline and at each subsequent time point, where applicable.

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

No descriptive statistics will be presented if n<4.

Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Summaries on PK population will be produced by product, and overall if applicable.

Summaries on Safety population will be produced overall and by sequence and study day (if applicable), including the available data from subjects who tested the product but were not enrolled or were discontinued from enrollment (back up subjects) before randomization. If there are more than 10 adverse events, then there will be an analysis by sequence and period, in addition.

The following product labels and sequence descriptions will be used throughout the TFLs (Table 12) :

**Table 12: Product and Sequence Labels**

| Product | Format used in TFLs | Order in TFLs |
|---|---|---|
| Carbon Heated Tobacco Product 1.1 Menthol | CHTP 1.1 M | 1 |
| Menthol conventional cigarettes | mCC | 2 |
| **Sequence** | | |
| Carbon Heated Tobacco Product 1.1 Menthol then Menthol conventional cigarettes | CHTP 1.1 M – mCC | 1 |
| Menthol conventional cigarettes then Carbon Heated Tobacco Product 1.1 Menthol | mCC - CHTP 1.1 M | 2 |

The following stratification labels (Table 13) for the TFLs will be used:

**Table 13: Stratification Labels**

| Stratification Factor | Definition |
|---|---|
| Sex | Male |
| | Female |
| ISO nicotine level | ≤ 0.6 mg |
| | > 0.6 to 1.0 mg |
| | > 1.0 mg[1] |

[1] Note that due to inclusion criteria for the study there should not be any subjects with ISO nicotine level > 1.0 mg, therefore this category will not be presented unless there is sufficient data for analysis/presentation (see Section 11.1.5.1 ”Insufficient Data for Analysis/Presentation”).

### 11.1.4 Definitions for Statistical Data Analysis

The following definitions (Table 14) for statistical analyses/presentations will be used:

**Table 14: Timepoint Definitions**

| Term | Definition |
|---|---|
| Baseline | Baseline is defined as the last available time point prior to $T_0$ on Day 1. Except for QSU, CO and COHb where the assessment prior to $T_0$ for each period will be used as a baseline. |
| $T_0$ | The time of the product use on Day 1 and Day 3, corresponding to the first puffing of CHTP 1.1 M or mCC. |

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

For questionnaire data total scores and domain or subscale scores may use a certain degree of imputation (by averaging across individual item scores) as detailed in Section 7.3 "Questionnaires".

In general, values below the lower limit of quantification (LLOQ) will be imputed using 0.5 x lower limit of quantification. For values above the upper limit of quantification (ULOQ), *i.e.*, preceded by a ">", for example ">xx," the numerical xx will be used for calculation and reporting in summary tables. The number and percent of values below LLOQ or above ULOQ will be presented in each summary table.

For the calculation of PK parameters, partial dates/times for PK assessments or $T_0$ will not in general be imputed. For time points recorded in the format hh:mm, instead of hh:mm:ss, the missing information on seconds will be imputed by 30 sec.

For PK concentration data:

1) Where there is a missing sample taken at 1 h post-exposure or later
   - and in the subsequent PK sample, nicotine is quantifiable the data will be analysed and reported as planned.
   - And in the subsequent PK sample, nicotine is not quantifiable (BQL) or the missing sample result occurs at 24 h post-exposure $AUC_{0\text{-last}}$ will, as well as being analysed and reported as planned, have a sensitivity analysis excluding those subjects.
2) Where there is a missing sample before 1 h post-exposure the parameters $C_{max}$ and $t_{max}$ will, as well as being analysed and reported as planned, have a sensitivity analysis excluding those subjects who have a missing sample before 1 h post-exposure.
3) Where the sample for the 15 min < $T_0$ time point is missing $AUC_{0\text{-t'}}$ will, as well as being analysed and reported as planned, have a sensitivity analysis excluding those subjects who have a missing sample at the 15 min < $T_0$ time point.
4) Where a subject was withdrawn at the 1 h post-exposure or later sample time, the only parameters to be reported would be $C_{max}$, $t_{max}$ and $AUC_{0\text{-t'}}$. All other parameters would be presented as NC (Not calculated) since only a limited partial concentration-

time profile is available and it is not comparable with the same parameters calculated for the other subjects and products and would therefore not be included in the statistical analysis.

5) If a subject is withdrawn < 1 h post-exposure, all PK parameters will be presented as NC.

For the PK concentrations below the quantification limit:

- LLOQ values before $T_0$ are considered as zero.
- LLOQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC).
- Any other LLOQ value (after $T_0$ and before the last quantifiable value) would need to be queried and, if confirmed, it will be imputed by LLOQ/2.

#### 11.1.5.1 Insufficient Data for Analysis/Presentation

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

Some of the TFLs may 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.”

Stratified summaries by sex or nicotine levels will not be presented if less than 4 subjects are available in one sex or nicotine levels strata.

### 11.1.6 Handling of Unplanned Data

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

### 11.1.7 Multiple Comparisons / Multiplicity

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

## 11.2 Disposition of Subjects

The number and percent of subjects will be summarized for the following categories: subjects screened, screening failed, enrolled subjects, enrolled and not randomized, randomized subjects, completed, and discontinued.

Inclusion and exclusion criteria will be listed as to whether the subjects have met or not met the criteria by sequence, subject, and study day (Screening and Admission).

Subjects in the Safety and PK populations will be displayed by sequence and overall.

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

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

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 – Screened Population |
| 15.2.1.2 | Summary of Reasons for Discontinuations – Randomized Population |
| 15.2.1.3 | Summary of Protocol Deviations – Safety Population |
| LISTINGS | |
| 15.3.1.1 | Listing of Inclusion/Exclusion Criteria |
| 15.3.1.7 | Listing of Subject Disposition and Assignment to Analysis Sets |
| 15.3.2.3 | Listing of Subjects and Observations Excluded from the PK Population and PK Analysis |
| 15.3.1.11 | Listing of Protocol Deviations |
| 16.1.7 | Listing of Randomization Scheme and Codes |

## 11.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety and PK populations, and listed for the Safety population.

The demographic variables age, sex, ethnicity, body weight, height and BMI will be summarized by sequence and overall for the Safety population.

Demographics will be tabulated overall and by the two stratification factors (sex and mCC nicotine level at Admission) for the PK populations, as specified in Section 11.1.1 “Stratified Presentation”.

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 – PK Population |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PK Population |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Nicotine Level –PK Population |
| LISTINGS | |
| 15.3.1.6 | Listing of Demographics |

### 11.3.1 CYP2A6 Activity at Admission

CYP2A6 activity will be calculated as the metabolite molar ratio of trans 3' hydroxycotinine and COT measured at Day-3 in plasma, as described in Section 7.2 "Biomarkers".

Data will be listed and summarized as reported in Section 11.3 "Demographics and Other 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 – PK Population |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PK Population |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Nicotine Level – PK Population |
| LISTINGS | |
| 15.3.1.10 | Listing of CYP2A6 Activity – Safety Population |

### 11.3.2 FTND Questionnaire at Screening

FTND score value and the number and percentage of subjects in each category (mild/moderate/severe) will be presented. Data will be listed and summarized as reported in Section 11.3 "Demographics and Other 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 – PK Population |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PK Population |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Nicotine Level – PK Population |
| LISTINGS | |
| 15.3.1.9 | Listing of Fagerström Test for Nicotine Dependence Results |

### 11.3.3 Current Cigarette and Smoking Characteristics

The following smoking characteristics at Admission (Day -3) will be summarized and listed as specified in Section 11.3 "Demographics and Other Baseline Characteristics": ISO tar yield (continuous and categorized as 1-5 mg, 6-8 mg, 9-10 mg and >10 mg), ISO nicotine level (continuous and categorized as ≤ 0.6 mg, > 0.6 to ≤ 1 mg, and > 1 mg), and number of mCCs smoked on a daily basis during the previous 4 weeks (categorized as < 10 cig/day, 10-19 cig/day and >19 cig/day).

Current mCC brand(s) smoked by the subject will be summarized and listed by sequence at Admission (Day -3) for the safety population. This will include brand name(s), and ISO nicotine and tar yields. The current mCC brand collected at Screening Visit will be listed only.

Smoking history, including whether subjects have smoked for at least the last three consecutive years, number of mentholated cigarettes smoked on average during the previous 4 weeks, and willingness to interrupt smoking up to 6 days will be listed by sequence at Screening and Admission (Day -3) Responses to planning to quit smoking during the next 3 months will be listed at Screening.

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 – PK Population |

| TFL number | Title |
|---|---|
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – PK Population |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Nicotine Level – PK Population |
| 15.2.1.5 | Summary of Current Cigarette Brands at Admission – Safety Population |
| LISTINGS | |
| 15.3.1.2 | Listing of Current Cigarette Brands |
| 15.3.1.3 | Listing of Smoking History |
| 15.3.1.4 | Listing of Product Test, Willingness to interrupt smoking up to 6 days, Willingness to Quit Smoking, |

### 11.3.4 Medical History and Concomitant Diseases

Medical history is defined as any condition that started and ended prior to Screening. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and listed separately by sequence, System Organ Class (SOC) and Preferred Term (PT) within SOC.

A concomitant disease is defined as any condition that started after ICF signature or was started prior to the Screening Visit and is still ongoing at the Screening Visit.. Concomitant disease will be coded using MedDRA version 18.0 and listed separately by sequence, SOC and PT within SOC.

Partial dates will not be imputed, but assumptions will be made as follows to assign to either medical history or concomitant diseases:

| Date information | Assign as |
|---|---|
| Missing stop date | Concomitant disease |
| Partial date, e.g., --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Screening. | Concomitant disease |
| Partial date, e.g., --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening. | Medical history |

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 | |
| 15.3.1.8 | Listing of Medical History and Concomitant Disease |

### 11.3.5 Other Data

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

- Urine cotinine test
- Urine pregnancy test
- Chest x-ray
- Urine drug screen
- Serology
- Alcohol breath test
- Prior and concomitant medication
- Product Test and Demonstration

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.1 | Summary of Subject Disposition – Screened Population |
| LISTINGS | |
| 15.3.1.4 | Listing of Product Test, Willingness to interrupt smoking up to 6 days, Willingness to Quit Smoking |
| 15.3.1.5 | Listing of Safety Laboratory Entry Criteria |
| 15.3.6.3 | Listing of Prior and Concomitant Medication |

## 11.4 Measurements of Product Compliance

Levels of CO in exhaled breath will be measured to evaluate the exposure to CO (see Section 11.6.2.2.1 “Exhaled CO and COHb”), and to monitor compliance during the following study days (see Section 6.3.3 “Compliance to Product Allocation”):

- Admission on Day -3
- Wash-out on Day -2/-1 and Day 2
- Single use Day 1 and Day 3
- Discharge on Day 4

CO data will be listed and summarized by sequence for all study days and timepoints as continuous variable and with the categorization ≤10 ppm and >10 ppm.

Values above 10 ppm will be highlighted in listings and be considered as non compliance if such values are observed prior to first product use on the single use days or during the washout days. CO data leading to exclusion of subjects from the analysis will be evaluated during the pre-analysis blind data review.

Number and percentage of subjects considered as non compliant during the study will be tabulated by sequence and study days for the Randomized population

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.9.1 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days Continuous Measurements– PK Population |
| 15.2.4.9.1.1 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days by Sex – PK Population |
| 15.2.4.9.1.2 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days by Nicotine Level – PK Population |
| 15.2.4.9.2 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days Categorical Measurements– PK Population |
| 15.2.4.10.1 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 Continuous Measurements– PK Population |
| 15.2.4.10.1.1 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 by Sex – PK Population |
| 15.2.4.10.1.2 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 by Nicotine Level – PK Population |
| 15.2.4.10.2 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 Categorical Measurements– PK Population |
| 15.2.5.1 | Descriptive Statistics of Compliance– Randomized Population |
| LISTINGS | |
| 15.3.3.4 | Listing of Exhaled Breath CO (ppm) and Measurement Times |

## 11.5 Extent of Exposure (Product Consumption)

Details of the product test prior to enrollment and of product use after randomization will be listed by sequence for the Safety population.

The number and percentage of subjects who smoked 1, 2, 3, 4 or 5 CHTP 1.1 M sticks at admission will be tabulated.

The number and percentage of subjects who smoked 0 or 1 (category >1 will be included if applicable) CHTP 1.1 M sticks, or mCC during single use days (Day 1 or Day 3) will be tabulated by sequence.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.2.1 | Descriptive Statistics of Product Use - Safety Population |
| LISTINGS | |
| 15.3.2.1 | Listing of Product Usage |

## 11.6 Planned Statistical Analyses

### 11.6.1 Primary Analyses

The primary parameters $C_{max}$ and $AUC_{(0\text{-last})}$ will be listed and summarized as described in Section 11.1 "General Considerations" and subsections. In addition plots of the data versus product will be provided.

The primary analysis of $C_{max}$ and $AUC_{(0\text{-last})}$ will be performed on the natural log-transformed parameters using an analysis of variance (ANOVA) model with terms for sequence, subject nested within sequence, period and product as fixed effect factors (**Senn, 2002**, **FDA, 2001**, **CHMP, 2010** and **CHMP Appendix IV, 2011**).

Carry-over effect will not be tested, as it cannot be statistically distinguished from the interaction between product and period in a 2x2 crossover design.

The SAS code to be used is shown below:

```
Proc glm data=_data_;
Class subject sequence product period;
Model log_pk = sequence subject(sequence) period product;
Lsmean product / pdiff =control('mCC') alpha=0.05 cl;
Test h=sequence e=subject(sequence);
Run;
```

where "log_pk" is the the natural log-transformed PK parameter being analyzed.

Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis".

LS means for each product will be back-transformed by exponentiation and will be tabulated together with the ratio (CHTP 1.1 M : mCC) and 95% CI.

The geometric CV will also be presented as $CV(\%) = 100\sqrt{(e^{MSE} - 1)}$, where MSE is the mean square error of the fitted model residual.

Exploratory subgroup analyses will be conducted for the primary endpoints in the following planned subgroups: sex (male or female), mCC nicotine level at Admission (ISO nicotine level ≤0.6 mg and >0.6 to ≤ 1mg) provided there are more than 4 subjects in each category.

In case of any nicotine levels at $T_0$ greater than 5% of their $C_{max}$ value being observed, a supportive analysis as described in Section 11.6.3 "Supportive/Sensitivity Analysis" of the primary endpoints will be performed as described above, where the data of these subjects with nicotine levels at $T_0$ greater than 5% of their $C_{max}$ value will be excluded from the analysis.

Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis" in order to evaluate the sensitivity of CHTP 1.1 M effect estimates to methods used for missing data by means of a mixed model approach, should there be 20% or more missing parameter PK values.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.3.1 | Analysis of Primary Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.3.2.1 | Analysis of Primary Pharmacokinetic Parameters of Nicotine by Sex– PK Population |
| 15.2.3.2.2 | Analysis of Primary Pharmacokinetic Parameters of Nicotine by Nicotine Level – PK Population |
| 15.2.4.4 | Descriptive Statistics of Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.4.4.1 | Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Sex – PK Population |
| 15.2.4.4.2 | Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Nicotine Level – PK Population |
| FIGURES | |
| 15.1.1.1 | Primary Pharmacokinetic Parameters of Nicotine vs. product – PK Population |
| LISTINGS | |
| 15.3.3.1 | Listing of Pharmacokinetic Parameters of Nicotine |
| 15.3.2.2 | Individual Efficacy Response Data |

### 11.6.2 Secondary Analyses

11.6.2.1 Pharmacokinetics

The secondary PK parameters ($AUC_{(0-12)}$, $AUC_{(0-t')}$, $AUC_{(0-\infty)}$, $\%AUC_{extrap}$, $t_{last}$, $t_{max}$, $\lambda_z$ and $t_{½}$) will be listed and summarized as described in Section 11.1 “General Considerations” and subsections. In addition plots of the data versus product will be provided.

The nicotine plasma concentrations will be summarized in a similar manner to the PK parameters but will also be split out by sample time point. Geometric mean (95% CI) profiles, spaghetti plots of all subjects and individual PK profiles for each subject will also be presented.

PK parameter and plasma concentration data will also be listed along with the details of the actual times after $T_0$.

Only subjects in the PK population who provide evaluable data for both the CHTP 1.1 M and mCC products will be included in the following analyses.

- The secondary analysis of $AUC_{(0-12)}$, $AUC_{(0-\infty)}$, $AUC_{(0-t')}$ and $t_{½}$ will be performed on the natural log-transformed parameters using the same ANOVA model as used for the primary analysis. (Section 11.6.1 "Primary Analyses").

- The analysis of $t_{max}$ will be performed by calculating the difference for each subject (CHTP 1.1 M - mCC) and obtaining the Hodges-Lehmann (**Hodges and Lehmann, 1963**) 95% CI estimates. The median $t_{max}$ for each product and the median difference between the products along with the 95% CI will be presented in the tables.

Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis" in order to evaluate the sensitivity of CHTP 1.1 M effect estimates to methods used for missing data by means of a mixed model approach, should there be 20% or more missing parameter PK model.

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.1 | Analysis of Secondary Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.4.4 | Descriptive Statistics of Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.4.4.1 | Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Sex – PK Population |
| 15.2.4.4.2 | Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Nicotine Level – PK Population |
| 15.2.4.5 | Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) – PK Population |
| 15.2.4.5.1 | Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) by Sex – PK Population |
| 15.2.4.5.2 | Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) by Nicotine Level – PK Population |
| FIGURES | |
| 15.1.2.1 | Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI – PK Population |
| 15.1.2.2 | Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects by Product – PK Population |
| 15.1.2.3 | Nicotine Plasma Concentration (ng/mL) Profiles by Subject – PK Population |
| 15.1.2.4 | Secondary Pharmacokinetic Parameters of Nicotine vs. product – PK Population |
| LISTINGS | |
| 15.3.3.1 | Listing of Pharmacokinetic Parameters of Nicotine |
| 15.3.3.2 | Listing of Additional Pharmacokinetic Parameter Data |

#### 11.6.2.2 Biomarkers

##### 11.6.2.2.1 Exhaled CO and COHb

COHb measured in blood and exhaled CO will be investigated as a measure of exposure to CO.

CO in exhaled breath will be measured using the Smokerlyzer® device such as Micro+™ Smokerlyzer® device or similar. A CO breath test will be conducted once at Day -3 and Day 4. On Day -2, Day -1, Day 1, Day 2, and Day 3, four CO breath tests will be done per day. On Day 1 and Day 3, the first test per day will be performed within 15 minutes prior to $T_0$ and then between 12:00 PM and 01:30 PM, between 4:00 PM and 05:30 PM, and between 8:00 PM and 09:30 PM. On the wash-out days (Day -2, -1 and Day 2) it will be conducted between 8:00 AM and 09:30 AM, 12:00 PM and 01:30 PM, between 4:00 PM and 05:30 PM, and between 8:00 PM and 09:30 PM.

Tests for COHb measurement will be performed at a local laboratory. Blood samples will be taken as follows at Day 1 and Day 3: a total of five blood samples will be taken. The first sample will be taken within 15 minutes prior to using the first product ($T_0$). Thereafter the sampling times in relation to $T_0$ are at 15 minutes, 60 minutes, 4 hours, and 12 hours post-$T_0$.

Descriptive statistics summarized by product will be produced separately for all scheduled timepoints for exhaled CO and COHb assessments at single use day. This will be done on the PK populations, overall and by the two stratification factors (sex, mCC nicotine level at Admission) as specified in Section 11.1.1 “Stratified Presentation”.

Actual values of blood COHb and levels of exhaled CO will be listed and summarized. The number of subjects with COHb levels ≤2% will be summarized for each measurement. The 2% threshold is important because, as reported in (**WHO, 2010**), COHb elevated above 2% was found to cause ST-segment changes and decreased time to angina.

In addition line graphs will be produced for exposure means (and 95% CI) over all timepoints.

Values of exhaled CO measured during wash-out, admission, and discharge will not be analyzed because they will be collected only for monitoring purposes, however they will be reported as described in Section 11.4 “Measurements of Product Compliance”.

The analysis of the exhaled CO during single use days and log transformed blood COHb levels will be performed using a mixed effects ANOVA with a restricted maximum likelihood (REML) method to estimate mean differences and variances for CHTP 1.1 M vs mCC, using unstructured covariance structure (Bethesda, 2013; Brown and Prescott,

1999). Subjects nested within sequence will be used as a random effects and sequence, period, product and product*time point will be used as fixed effect factors. The model will be evaluated including all of the different assessment timepoints, excluding the assessment prior to $T_0$, In addition, time point will be treated as a repeated measurement.

The SAS code to be used is shown below:

```
Proc mixed data=_data_ method=reml maxiter=200;
Class subject sequence product period time_point;
Model log_COHb (or CO) = sequence period product time_point
product*time_point;
Random subject(sequence);
Repeated time_point / subject=subject*product type=un;
Lsmean product / pdiff =control('mCC') alpha=0.05 cl;
Lsmean product*time_point / pdiff alpha=0.05 cl;
Run;
```

In case of model convergence issues, this will be reported in the study report and additional covariance structures will be investigated with the following order: heterogeneous compound symmetry (type=csh), heterogeneous autoregressive (`type=arh`) and variance component (`type=vc`).

For the analysis of CO breath test, the main comparison will be the difference over all time points. LS means for each product, the overall difference and the differences at each time point will be presented in the tables as a point and interval (95% CI) estimate. Figures of the LS mean difference and 95% CI at each time point will be produced.

For the COHb analysis, the main comparison will be the ratio over all time points. LS means for each product will be back-transformed by exponentiation and presented in tables together with the point and interval (95% CI) estimate of the overall ratio and of the ratios at the different time points. Figures of the LS mean ratio and 95% CI at each time point will be produced.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.6 | Analysis of Blood COHb (%) – PK Population |
| 15.2.4.7.1 | Descriptive Statistics of Blood COHb (%) Continuous Measurements – PK Population |
| 15.2.4.7.1.1 | Descriptive Statistics of Blood COHb (%) by Sex – PK Population |
| 15.2.4.7.1.2 | Descriptive Statistics of Blood COHb (%) by Nicotine Level – PK Population |
| 15.2.4.7.2 | Descriptive Statistics of Blood COHb (%) Categorical Measurements – PK Population |
| 15.2.4.8 | Analysis of Exhaled CO (ppm) During Single Use Days – PK Population |

| TFL number | Title |
|---|---|
| 15.2.4.9.1 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days Continuous Measurements – PK Population |
| 15.2.4.9.1.1 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days by Sex – PK Population |
| 15.2.4.9.1.2 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days by Nicotine Level – PK Population |
| 15.2.4.9.2 | Descriptive Statistics of Exhaled CO (ppm) During Single Use Days Categorical Measurements– PK Population |
| 15.2.4.10.1 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 Continuous Measurements – PK Population |
| 15.2.4.10.1.1 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 by Sex – PK Population |
| 15.2.4.10.1.2 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 by Nicotine Level – PK Population |
| 15.2.4.10.2 | Descriptive Statistics of Exhaled CO (ppm) During Days -3,-2, -1, 2 and 4 Categorical Measurements– PK Population |
| FIGURES | |
| 15.1.2.5.1 | Blood COHb (%) Profiles Geometric Mean and 95% CI –PK Population |
| 15.1.2.6.1 | Blood COHb (%) Profiles Geometric Least Squares Mean Ratio and 95% CI –PK Population |
| 15.1.2.7.1 | Exhaled CO (ppm) Profiles During Single Use Days Arithmetic Mean and 95% CI –PK Population |
| 15.1.2.8.1 | Exhaled CO (ppm) Profiles During Single Use Days Arithmetic Least Squares Mean Differences and 95% CI –PK Population |
| LISTINGS | |
| 15.3.3.3 | Listing of Blood COHb Levels (%) and Sampling Times |
| 15.3.3.4 | Listing of Exhaled Breath CO (ppm) and Measurement Times |

11.6.2.3 Questionnaires

11.6.2.3.1 Urge-to-Smoke Questionnaire of Smoking Urges Brief

The total score and the two factors from the QSU-brief will be listed for all scheduled time points and summarized overall and by the two stratification factors (sex, mCC nicotine level at Admission) for the PK population, as specified in Section 11.1.1 “Stratified Presentation”. This will also be done for the changes from baseline, the percent change from baseline and the maximum percent decrease over time. The percent change and the time to maximum percent decrease in total score will be summarized by product and analyzed using the Hodges-Lehmann method. The individual responses to all questions will be listed by product, study day, and assessment time points.

In addition line graphs will be produced for the total score and factors means (and 95% CI) over all timepoints.

The analysis of the subjective effects of smoking (the total score, and Factor-1 and Factor-2 from the QSU-brief) will be performed using the same mixed effects ANOVA

adopted for the analysis of CO breath test described in Section 11.6.2.2.1 "Exhaled CO and COHb", including also the baseline score.

The main comparison will be the mean difference over all timepoints. LS means for each product, the overall mean difference and the mean differences at each time point will be presented in the tables as a point and interval (95% CI) estimate. Figures of the LS mean difference and 95% CI at each time point will be produced.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.11 | Analysis of QSU-brief Questionnaire Factors and Total Score – PK Population |
| 15.2.4.12 | Analysis of the Time to Maximum Percent Decrease in Total Score – PK Population |
| 15.2.4.13 | Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score – PK Population |
| 15.2.4.13.1 | Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score by Sex – PK Population |
| 15.2.4.13.2 | Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score by Nicotine Level – PK Population |
| 15.2.4.14 | Descriptive Statistics of Time to Maximum Decrease in Total Score – PK Population |
| 15.2.4.14.1 | Descriptive Statistics of Time to Maximum Decrease in Total Score by Sex – PK Population |
| 15.2.4.14.2 | Descriptive Statistics of Time to Maximum Decrease in Total Score by Nicotine Level – PK Population |
| FIGURES | |
| 15.1.2.9.1 | QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI PK Population |
| 15.1.2.10.1 | QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences and 95% CI –PK Population |
| LISTINGS | |
| 15.3.6.11 | Listing of QSU-brief Questionnaire Results |

11.6.2.3.2 Modified Cigarette Evaluation Questionnaire

The MCEQ domain scores composed of the three multi-item subscales and two single items from the MCEQ will be listed and summarized overall and by the two stratification factors (sex, mCC nicotine level at Admission) for the PK populations, as specified in Section 11.1.1 "Stratified Presentation". The individual responses to all questions will be listed.

A mixed effects ANOVA model will be used to estimate mean CHTP 1.1 M - mCC differences of the MCEQ domain scores and variances, with a REML method (Bethesda,

2013; Brown and Prescott, 1999). Subjects within sequence will be used as random effects and fixed effects are period, sequence, and product exposure.

```
Proc mixed data=_data_ method=reml maxiter=200;
Class subject sequence product period;
Model response = sequence period product;
Random subject(sequence);
Lsmean product / pdiff =control('mCC') alpha=0.05 cl;
Run;
```

LS means for each product and the overall point and 95% interval estimate of the difference will be presented in the tables.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.15 | Analysis of MCEQ Subscales – PK Population |
| 15.2.4.16 | Descriptive Statistics of MCEQ Subscales – PK Population |
| 15.2.4.16.1 | Descriptive Statistics of MCEQ Subscales by Sex – PK Population |
| 15.2.4.16.2 | Descriptive Statistics of MCEQ Subscales by Nicotine Level – PK Population |
| LISTINGS | |
| 15.3.6.12 | Listing of MCEQ Questionnaire Results |

### 11.6.3 Supportive/Sensitivity Analysis

To better understand the impact of the higher than expected $T_0$ values, an analysis of the PK parameters will be performed as described above, however the data for subjects with their $T_0$ value >5% of their $C_{max}$ value will be excluded from the analysis. To support the interpretation of the PK analysis, the values of nicotine concentration greater than BLOQ before $T_0$ will be listed together with any PK parameters excluded from the analysis. Listings will be presented by PK parameter, sequence, period and study date.

Sensitivity analysis will be conducted on the $C_{max}$ and $AUC_{(0\text{-last})}$ endpoints for the PK population should there be 20% or more missing PK parameter values. This analysis is conducted on all the available PK parameters and subjects will be excluded from the analysis if 20% or more of their PK parameter values are missing. The analysis will be conducted in the natural log scale using mixed effects ANOVA model including period, sequence, and product exposure as fixed effects and subject wihtin sequence as a random effect. Point and 95% interval estimates of the ratios will be back-transformed by exponentiation and tabulated.

Sensitivity analysis will be conducted following the model described in 11.6.1 “Primary Analyses” in case of missing data as described in Section 11.1.5 “Handling of Dropouts or Missing Data (including outside the limits of quantification)”:

1) Where there is a missing sample taken at 1 h post-exposure or later and in the subsequent PK sample, nicotine is not quantifiable (BQL) or the missing sample result occurs at 24 h post-exposure $AUC_{0\text{-last}}$ will, as well as being analysed and reported as planned, have a sensitivity analysis excluding those subjects.
2) Where there is a missing sample before 1 h post-exposure the parameters $C_{max}$ and $t_{max}$ will, as well as being analysed and reported as planned, have a sensitivity analysis excluding those subjects who have a missing sample before 1 h post-exposure.
3) Where the sample for the 15 min < $T_0$ time point is missing $AUC_{0\text{-t'}}$ will, as well as being analysed and reported as planned, have a sensitivity analysis excluding those subjects who have a missing sample at the 15 min < $T_0$ time point.

In case any time information is imputed for the computation of PK parameters as described in Section 11.1.5 "Handling of Dropouts or Missing Data (including outside the limits of quantification)" in any PK population, the median $t_{max}$ for CHTP 1.1 M will be calculated following the imputation of missing time data by 0 sec and 30 sec. If the difference between the two median $t_{max}$ is larger than 5%, a supportive analysis will be conducted by repeating the analyses described in Section 11.6.1 "Primary Analyses" and 11.6.2.1 "Pharmacokinetics" on the $t_{max}$, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{- t'})}$ endpoints estimated by means of the imputation of missing time by 0 sec.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| Table 15.2.4.2.1 | Analysis of Pharmacokinetic Parameters of Nicotine: sensitivity analysis: missing data - PK Population |
| Table 15.2.4.2.2 | Analysis of Pharmacokinetic Parameters of Nicotine: sensitivity analysis: quantifiable predose concentrations - PK Population |
| Table 15.2.4.2.3 | Analysis of Pharmacokinetic Parameters of Nicotine: sensitivity analysis: missing concentrations – PK Population |
| Table 15.2.4.3 | Analysis of Pharmacokinetic Parameters of Nicotine by Zero Sec Imputation – PK Population |

### 11.6.4 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 VAS and Likert scales).

The primary analysis of Safety parameters will be conducted on the Safety population as described in Section 11.1.3 "Descriptive Statistics".

11.6.4.1 Safety Reporting

An exposure 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.

Any AEs which occur during the Screening Period will be captured by the site collaborators and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study procedures. All collected AEs will be reported in the CSR and will be in accordance with the respective regulatory guidelines. 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). All AEs occurring after the product test of CHTP 1.1 M or mCC will be included in the summary tables. During the screening period prior to the first CHTP 1.1 M or mCC product use, only study procedure related AEs will be listed only.

AEs reported from enrolled subjects, but not started use on day 1 or later will be summarized in a separate sequence: “Enrolled but not started randomized product use”. Furthermore AEs reported after discharge (Day 4) are summarized in a separate sequence ‘safety follow-up’.

If there are more than 10 AEs, the tables will also be split by study period. The study periods will be defined as in **Table 15**:

**Table 15: Study Periods**

| Period | Period Start | Period End |
|---|---|---|
| Screening | Date of informed consent | Day -4 |
| CHTP 1.1 M Product Test | Day -3 | Day -1 |
| Study Period 1 | Day 1 | Day 2 |
| Study Period 2 | Day 3 | Day4 |
| Safety Follow-Up | Day 5 | EOS |

Partial dates will not be imputed, but assumptions will be made as follows to assign to exposure-emergent or not:

| Date information | Assign as |
|---|---|
| Partial date, e.g., --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of first product use | Exposure-emergent |
| Partial date, e.g., --May2012, or -----2011. If month and/or year is earlier than the month and/or year of first product use | Not exposure-emergent |

If exposure emergent adverse events cannot be attributed to CHTP 1.1 M / mCC due to e.g. missing start time, the worst case principle will be applied : i.e. the event will be allocated to CHTP 1.1 M use.

#### 11.6.4.2 Adverse Events

A general summary table of AEs will be presented by sequence (and period if more than 10 AEs) and overall, 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 AE leading to death.
- 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 CHTP 1.1 M / mCC) and expectedness (expected, not expected).
- The number of events and the number and percentage of subjects reporting at least one AE broken down by severity, including a subject once with worst severity.
- 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 (combining the following items: product use interrupted, product use reduced, product use stopped), 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.

Additional summary tables of AEs will be presented by sequence (and period if more than 10 AEs) and overall, 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 18.0):

- 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 AE leading to death.
- The number of events and the number and percentage of subjects with at least one AE related to product exposure and expectedness for investigational product (IP;CHTP 1.1 M or mCC).
- The number of events and the number and percentage of subjects with at least one AE leading to study discontinuation.
- The number of events and the number and percentage of subjects with at least one AE related to study procedure.
- The number of events and the number and percentage of subjects with at least one AE by severity (mild, moderate, severe)

If a subject has more than one occurrence of the same AE, the subject will be counted only once within a PT for each sequence, 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 |
| 15.2.6.2.1 | Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.2.2 | Summary of Adverse Events by System Organ Class – Safety Population |
| 15.2.6.2.3 | Summary of Adverse Events by Preferred Term – Safety Population |
| 15.2.6.3 | Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure for Investigational Product (CHTP 1.1 M or mCC)– Safety Population |
| 15.2.6.4 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.5 | Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.6 | Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population |
| LISTINGS | |
| 15.3.6.1.1 | Listing of Adverse Events |
| 11.6.4.2.1 | Serious Adverse Events (Including Deaths) |

A general summary table of SAEs will be presented by sequence (and period if more than 10 AEs) and overall, including the number of events and the number and percentage of subjects reporting at least one SAE.

SAEs will be listed in separate listings by sequence.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| LISTINGS | |
| 15.3.6.1.2 | Listing of Serious Adverse Events |

#### 11.6.4.2.2 Adverse Events Leading to Withdrawal

Summaries will be presented for AEs leading to withdrawal, by sequence (and period if more than 10 AEs) and overall AEs leading to withdrawal will also be listed in separate listings by sequence.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| LISTINGS | |
| 15.3.6.1.3 | Listing of Adverse Events Leading to Discontinuation |

#### 11.6.4.2.3 Laboratory Abnormalities

Laboratory abnormality data will be listed ordered by sequence, subject and time point. Details related to the toxicity grading of laboratory abnormalities are available in Section 11.6.4.4 “Clinical Laboratory Evaluation”.

| TFL number | Title |
|---|---|
| LISTINGS | |
| 15.3.6.4 | Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.5 | Listing of Hematology Data, Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.6 | Listing of Urinalysis Data, Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.1.3 | Listing of Adverse Events Leading to Discontinuation |

### 11.6.4.3 Investigational Product Malfunction and Misuse

All events relating to CHTP 1.1 M Malfunction and Misuse will be listed for each subject, including event description and onset datetimes.
A summary table of CHTP 1.1 M Malfunction and Misuse will be presented by sequence and overall, including:

- Number of CHTP 1.1 M Malfunction and Misuse events and the number and percentage of subjects reporting at least one event.
- Number of CHTP 1.1 M Malfunction and Misuse events and the number and percentage of subjects categorized by event description (Defect CHTP 1.1 M before use, Defect CHTP 1.1 M during decapping, Defect CHTP 1.1 M during use, other)

CHTP 1.1 M Malfunction and Misuse events and inventory will be listed by sequence. Data collected during Screening will be listed but not summarized.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.7 | Summary of CHTP 1.1 M Malfunction and Misuse events– Safety Population |
| LISTINGS | |
| 15.3.6.2 | Listing of CHTP 1.1 M Malfunction and Misuse events |

11.6.4.4 Clinical Laboratory Evaluation

Table 16 lists the hematology, clinical chemistry, and urine analysis parameters to be assessed in this study.

**Table 16: 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 |
| | Aspartate aminotransferase | RBC traces |
| Mean corpuscular volume | Blood urea nitrogen | Protein |
| Platelet count | Creatinine | Specific gravity |
| Red blood cell (RBC) count | Gamma-glutamyltransferase | |
| White blood cell (WBC) count | Fasting glucose | |
| Differential WBC count: | Lactate dehydrogenase | |
| • Neutrophils | Potassium | |
| • Basophils | Sodium | |
| • Eosinophils | Total bilirubin | |
| • Lymphocytes | Direct bilirubin | |
| • Monocytes | Total cholesterol | |
| | Triglycerides | |

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the 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 after screening 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 AEs. These CTCAE grades will be derived programmatically in the creation of the SDTM datasets.

Laboratory data will be summarized and listed at screening, baseline (Admission, Day -3) and at discharge (Day 4 or at the day of withdrawal), together with changes from baseline. The number and percentage of subjects with normal results, high/low results and abnormal clinical result (as defined by PI comment) will be tabulated for laboratory parameters.

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

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.10 | Summary of Clinical Chemistry Parameters – Safety Population |
| 15.2.6.11 | Summary of Hematology Parameters – Safety Population |
| 15.2.6.12 | Summary of Urinalysis Parameters – Safety Population |
| LISTINGS | |
| 15.3.6.4 | Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.5 | Listing of Hematology Data Shift, Changes from Baseline and CTCAE grades |
| 15.3.6.6 | Listing of Urinalysis Data Shift, Changes from Baseline and CTCAE grades |

11.6.4.5 Vital Signs, Physical Findings and Other Observations Related to Safety

11.6.4.5.1 Prior and Concomitant Medication

Prior medication is defined as any medication taken within 4 weeks prior to Screening. Any medication which was started prior to the Screening Visit and is still being taken by the subject will be considered as concomitant medication. Medication initiated after the Screening Visit is also referred to as concomitant medication.

All medications will be listed by sequence using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization - Drug Dictionary Enhanced [WHO-DDE] March 2015 C format). A flag will be presented on the listing indicating whether the medication is prior or concomitant. Partial dates will not be imputed, but assumptions will be made as follows to assign to either prior or concomitant medications:

| Date information | Assign as |
|---|---|
| Missing stop date | Concomitant |
| Partial date, e.g., --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Screening. | Concomitant |
| Partial date, e.g., --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening. | Prior |

Prior and concomitant medications will be listed by sequence. Concomitant medications will be summarized for the Safety population showing the number (%) of subjects who used the medication at least once by sequence and by ATC 1st and 2nd levels medical term and by preferred drug name. Listings will be provided by sequence and will display original dates (no imputation).

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.8.1 | Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population |
| 15.2.6.8.2 | Summary of Prior Medication by Preferred Drug Name – Safety Population |
| 15.2.6.9.1 | Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population |
| 15.2.6.9.2 | Summary of Concomitant Medication by Preferred Drug Name – Safety Population |
| LISTINGS | |
| 15.3.6.3 | Listing of Prior and Concomitant Medication |

11.6.4.5.2 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -3) and at discharge (Day 4 or at the day of withdrawal for withdrawn subjects) will be listed by sequence. Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. Number of subjects (%) with normal, abnormal, and abnormal clinically significant results will be tabulated by body systems at Screening, baseline (Admission), and discharge.

Body weight recorded at the Screening visit, Admission and discharge; and body height recorded at the Screening visit will also be listed together with BMI. Descriptive statistics

of body weight, body height and BMI (BMI will also be categorized as shown in Section 7.4") will be tabulated for Admission and discharge.

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

Categorical Variables, at the Screening visit, Admission and discharge, will be presented by sequence and overall.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.16 | Summary of Weight and BMI Measurements – Safety Population |
| 15.2.6.17 | Summary of Physical Examination of Body Systems – Safety Population |
| LISTINGS | |
| 15.3.6.10 | Listing of Physical Examination Findings, Shift and Changes from Screening |

11.6.4.5.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate measured during the study will be listed by sequence and study day.

Descriptive statistics will be presented for systolic and diastolic blood pressure, pulse rate and respiratory rate at baseline, and on every subsequent day of the confinement period by sequence 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 | |
| 15.2.6.13 | Summary of Vital Signs – Safety Population |
| LISTINGS | |
| 15.3.6.7 | Listing of Vital Signs Data and Changes from Baseline |

11.6.4.5.4 Spirometry

Spirometry parameters assessed during the study include:

- Measured forced expiratory volume in 1 second ($FEV_1$)
- Measured forced vital capacity (FVC)
- $FEV_1$/FVC
- Predicted $FEV_1$
- Best measured $FEV_1$
- Percent of predicted $FEV_1$ (% pred)
- Predicted FVC
- Best measured FVC
- Percent of predicted FVC (% pred)

• Measurement interpretation (categories: normal, abnormal not clinically significant, abnormal clinically significant)

The above data are collected at Screening, Admission and discharge. At Screening, data are collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator.

Spirometry data values and normality evaluation will be listed by sequence and study day. Assessments performed after baseline (Admission, discharge) 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 $FEV_1$(L), $FEV_1$(% pred), FVC(L), FVC(% pred), and $FEV_1$/FVC at admission and discharge by sequence, and overall. Spirometry 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 | |
| 15.2.6.15 | Summary of Spirometry Measurements – Safety Population |
| LISTINGS | |
| 15.3.6.8 | Listing of Spirometry Data and Changes from Baseline |

11.6.4.5.5 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 QT interval corrected using Bazett's formula (QTcB) and Fridericia's formula (QTcF) intervals; QRS duration; heart rate; and normality evaluation (normal, abnormal not clinically relevant, abnormal clinically relevant, together with any PI comments about the abnormality). In addition the QTcF value will be presented.

ECG data values and normality evaluations will be listed by sequence and study day (Screening, Day 1, and Day 3) together with changes and shift in normality from baseline (Screening). ECG data from subjects which had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for ECG data at baseline, Day 1, and Day 3 by sequence and overall. ECG data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinical significant results.

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.14 | Summary of ECG Measurements – Safety Population |
| LISTINGS | |
| 15.3.6.9 | Listing of ECG Data and Changes from Baseline |

11.6.4.5.6 Assessment of Cough

Cough questionnaire is assessed from Day -2/-1 to Day 4, prior to product use on Day 1 and Day 3. Questionnaire details are reported in Section 7.3.4 “Cough Assessment”.

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

The data will be presented in the below outputs:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.18 | Summary of Cough Assessments – Safety Population |
| 15.2.6.18.1 | Summary of Cough Assessments by Study Day – Safety Population |
| LISTINGS | |
| 15.3.6.13 | Listing of Cough Assessment Results |

# 12 ANALYSIS AND REPORTING

## 12.1 Interim Analysis and Data Monitoring

No interim analysis is planned on this study.

A Clinical Research Associate (“Monitor”) from [redacted] will be responsible for the monitoring of the study. Monitoring will be performed according to [redacted] 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.

## 12.2 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 no. | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.2.1 | Descriptive Statistics of Product Use - Safety Population |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| 15.2.6.2.1 | Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.3 | Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Product Exposure for Investigational Product (CHTP 1.1 M or mCC) – Safety Population |
| 15.2.6.7 | Summary of CHTP 1.1 M Malfunction and Misuse events – Safety Population |
| LISTINGS | |
| 15.3.6.1.2 | Listing of Serious Adverse Events |
| 15.3.6.1.3 | Listing of Adverse Events Leading to Discontinuation |

## 12.3 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 no. | Title |
|---|---|
| TABLES | |
| 15.2.3.1 | Analysis of Primary Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.4.1 | Analysis of Secondary Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.4.4 | Descriptive Statistics of the Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.2.4.5 | Descriptive Statistics of Plasma Nicotine Concentrations – PK Population |
| 15.2.4.11 | Analysis of QSU-brief Questionnaire Factors and Total Score – PK Population |
| 15.2.4.13 | Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score – PK Population |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| 15.2.6.2.1 | Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |

| TFL no. | Title |
|---|---|
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – PK Population |
| FIGURES | |
| 15.1.1.1 | Primary Pharmacokinetic Parameters of Nicotine – PK Population |
| 15.1.2.1 | Nicotine Plasma Concentration (units) Profiles Geometric Mean and 95% CI – PK Population |
| 15.1.2.9.1 | QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI – PK Population |
| 15.1.2.10.1 | QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences and 95% CI – PK Population |

### 12.4 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.

### 12.5 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 no. | Title |
|---|---|
| TABLES | |
| 15.2.1.1 | Summary of Subject Disposition – Screened Population |
| 15.2.4.17 | Descriptive Statistics of Sex, Age, and Nicotine Level – PK Population |
| 15.2.3.3 | Analysis of Pharmacokinetic Parameters of Nicotine $C_{max}$, $AUC_{(0\text{-last})}$, $t_{max}$ – PK Population |

## 13 DATA PRESENTATION

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

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# 15 APPENDICES

## 15.1 Study Assessments

| | Screening | Admission | Wash-out | Single Use | Wash-out | Single Use | Discharge [k] | Safety Follow-up [l] |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-31 to -4** | **-3** | **-2/-1** | **1** | **2** | **3** | **4** | **4 to 11** |
| Informed consent | ● | | | | | | | |
| Information on the risks of smoking/smoking cessation advice, and debriefing | ● | ● | | | | | ● | |
| Inclusion/exclusion criteria | ● | ● | | | | | | |
| Enrolment | | ● | | | | | | |
| Randomization | | | ● | | | | | |
| Single product use | | | | ● | | ● | | |
| Support during periods of reduced smoking/smoking abstinence (as required) | | | ● | ● | ● | ● | | |

| | Screening | Admission | Wash-out | Single Use | Wash-out | Single Use | Discharge [k] | Safety Follow-up [l] |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-31 to -4** | **-3** | **-2/-1** | **1** | **2** | **3** | **4** | **4 to 11** |
| Product demonstration of CHTP 1.1 M | ● | | | | | | | |
| Product test for CHTP 1.1 M | | ● | | | | | | |
| Identification of current mCC brand | ● | ● | | | | | | |
| Smoking history | ● | | | | | | | |
| Readiness to accept interruption from smoking up to 6 days | ● | ● | | | | | | |
| Willingness to quit smoking in the next 3 months | ● | | | | | | | |
| X-ray [a] | ● | | | | | | | |
| Demographics [b], medical history, concomitant diseases | ● | | | | | | | |
| Prior medication[c]/Concomitant | ● | ● | ● | ● | ● | ● | ● | ● |

| | Screening | Admission | Wash-out | Single Use | Wash-out | Single Use | Discharge [k] | Safety Follow-up [l] |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-31 to -4** | **-3** | **-2/-1** | **1** | **2** | **3** | **4** | **4 to 11** |
| medication | | | | | | | | |
| Physical examination, body height, weight and BMI [d] | ● | ● | | | | | ● | |
| Vital signs [e] | ● | ● | ● | ● | ● | ● | ● | |
| ECG | ● | | | ● | | ● | | |
| Spirometry | ● | ● | | | | | ● | |
| B/U: Hematology, clinical chemistry, urine analysis | ● | ● | | | | | ● | |
| B: Serology | ● | | | | | | | |
| U: Urine drug screen, urine cotinine screen | ● | ● | | | | | | |
| Alcohol breath test | ● | ● | | | | | | |
| U: Pregnancy test | ● | ● | | | | | ● | |
| Collection of used CHTP | | ● | | ● | | ● | | |

| | Screening | Admission | Wash-out | Single Use | Wash-out | Single Use | Discharge [k] | Safety Follow-up [l] |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-31 to -4** | **-3** | **-2/-1** | **1** | **2** | **3** | **4** | **4 to 11** |
| 1.1 M and mCC butts | | | | | | | | |
| B: Plasma nicotine [f] | | | | ● | ● | ● | ● | |
| B: COHb [g] | | | | ● | | ● | | |
| CO breath test [h] | | ● | ● | ● | ● | ● | ● | |
| *trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma | | ● | | | | | | |
| FTND questionnaire | ● | | | | | | | |
| QSU–brief questionnaire [i] | | | | ● | | ● | | |
| MCEQ (modified version) | | | | ● | | ● | | |
| Cough assessment [j] | | | ● | ● | ● | ● | ● | |
| AE/SAE recording | ● | ● | ● | ● | ● | ● | ● | ● |

Abbreviations:

AE = adverse event; mCC = menthol conventional cigarette(s); CHTP 1.1 M = Carbon Heated Tobacco Product 1.1 Menthol; CO = carbon monoxide; COHb = carboxyhemoglobin; CYP2A6 = Cytochrome P450 2A6; ECG = electrocardiogram; FTND = Fagerström test for nicotine dependence (revised version); MCEQ = modified cigarette evaluation questionnaire; QSU-brief = questionnaire of smoking urges; SAE = serious adverse event.

B: blood sample required. U: urine sample required.

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

b: Sex, date of birth/age.

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

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

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

f: Nicotine blood samples (n=16) to be taken as follows:

The first blood sample will be taken within 15 minutes prior to the product use ($T_0$). Thereafter in relation to $T_0$, blood will be drawn at the following time points: $T_1$ after 2 min + 1 min, $T_2$ after 4 min + 1min, $T_3$ after 6 min + 1 min, $T_4$ after 8 min + 1 min, $T_5$ after 10 min + 1 min, $T_6$ after 15 min + 2 min, $T_7$ after 30 min + 2 min, $T_8$ after 45 min + 2 min, $T_9$ after 60 min + 3 min, $T_{10}$ after 2 hours + 5 min, $T_{11}$ after 4 hours + 5 min, $T_{12}$ after 6 hours + 5 min, $T_{13}$ after 9 hours + 5 min, $T_{14}$ after 12 hours + 5 min, and $T_{15}$ after 24 hours + 5 min. Cotinine will be measured in the same sample with the same assay together with nicotine. No additional sample for cotinine is required.

g: COHb blood samples (n=5) to be taken as follows:

The first sample within 15 minutes prior to $T_0$; thereafter in relation to $T_0$ at 15 min + 2 min, 60 min + 3 min, 4 hours + 5 min and 12 hours + 5 min

h: A CO breath test will be conducted once on Day -3 and Day 4. On Day -2, Day -1, Day 1, Day 2, Day 3, four breath tests will be done per day. On Day 1 and Day 3, the first test per day will be performed within 15 minutes prior to $T_0$ and then around 12:00 pm, 4:00 pm and 8:00 pm.

i: QSU–brief will be assessed as follows:

The QSU-brief will be completed by the subject himself/herself at single use study days. The first assessment will be done prior to $T_0$. All other assessments will be done after $T_0$, at 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours (with an allowed time window of +5 min each) and 4 hours, 6 hours, 9 hours, 12 hours (with an allowed time window of +10 min each).

j: Visual analogue scale, three Likert scales and one open question. Cough questionnaire should be asked on Day -1 between 06:30 and 09:00; on Day 2: 24 hours after $T_0$ of Day 1; on Day 4: 24 hours after $T_0$ of Day 3; and on Day 1 and Day 3: prior to product use.

k: All examinations listed at Discharge should also be conducted in subjects prematurely terminating the study.

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