# STATISTICAL ANALYSIS PLAN

## A randomized, controlled, open-label, 2-arm parallel group, single center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Carbon Heated Tobacco Product 1.0 (CHTP 1.0) compared to continuing to use conventional cigarettes during 5 days in confinement.

Study Product: Carbon Heated Tobacco Product 1.0 (CHTP 1.0)

Sponsor Reference No.: P2R-REXC-06-EU

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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 4.0 dated 24 June 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 TFLs template document. Any changes to the TFL shells numbering or to the title of the TFLs will not require an amendment to this SAP.

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

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

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (**ICH Guideline E9, 1998**).
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" **(ICH Guideline E3, 1995**).
- Electronic case report forms (eCRF) Version 4.0 dated 25 June 2015.
- Biostatistical Addendum – Subject Randomization List version 3.0 (14 Sep 2015).

## 3.1 Revision History

| Version | Date of Revision | Revision |
|---|---|---|
| 1.0 | 8 Feb 2016 | Final Version 1 |
| 2.0 | 21 Mar 2016 | Clarification in section 11 "Protocol Deviations" of the major and minor protocol deviations.<br>Correction in section 11.3 of the assessment windows to reflect the protocol defined assessment windows. |

# 4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used within this SAP.

| | |
|---|---|
| 1-NA | 1-aminonaphthalene |
| 1-OHP | Total 1-hydroxypyrene |
| 2-NA | 2-aminonaphthalene |
| 3-HPMA | 3-hydroxypropylmercapturic acid |
| 4-ABP | 4-aminobiphenyl |
| ADaM | Analysis Data Model |
| AE/SAE | Adverse Event/ Serious Adverse Event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic and Chemical |
| AUQ | Above upper limit of quantification |
| B[a]P | 3-hydroxybenzo(a)pyrene |
| BMI | Body Mass Index |
| BoExp | Biomarkers of exposure |
| CAF | Caffeine |
| CC | Conventional Cigarettes |
| CEMA | 2-cyanoethylmercapturic acid |
| CHTP | Carbon Heated Tobacco Product |
| CI | Confidence Interval |
| CO | Carbon Monoxide |
| COHb | Carboxyhaemoglobin |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events and Common Toxicity Criteria |
| CV | Coefficient of Variation |
| CYP1A2 | Cytochrome P450 1A2 |
| CYP2A6 | Cytochrome P450 2A6 |
| ECG | Electrocardiogram |
| EOS | End of Study |
| FAS | Full Analysis Set |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FTND | Fagerström Test for Nicotine Dependence |
| FVC | Forced Vital Capacity |
| HEMA | 2-hydroxyethyl mercapturic acid |
| HIV | Human Immunodeficiency Virus |
| HMPMA | 3-hydroxy-1-methylpropyl-mercapturic acid |
| HPT | Human Puffing Topography |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ISO | International Organization for Standardization |
| IXRS | Interactive Web Response System |

| | |
|---|---|
| LLOQ | Lower Limit of Quantification |
| LS | Least Squares |
| MCEQ | Modified Cigarette Evaluation Questionnaire |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHBMA | Monohydroxybutenyl mercapturic acid |
| MNWS | Minnesota Nicotine Withdrawal Scale |
| MR | Mean Ratio |
| NEQ | Nicotine Equivalents |
| NNAL | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol |
| NNN | Total N-nitrosonornicotine |
| NSAIDS | nonsteroidal anti-inflammatory drugs |
| o-tol | O-toluidine |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| PT | Preferred Term |
| PX | Paraxanthine |
| QC | Quality Control |
| QSU-brief | Urge-to-Smoke Questionnaire of Smoking Urges Brief |
| QTcB | QT Interval Corrected using Bazett's Formula |
| QTcF | QT Interval Corrected using Fridericia's Formula |
| SA | Smoking Abstinence |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SDTM | Standard Data Tabulation Module |
| SMAR | Smoking article |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| S-BMA | S-benzylmercapturic acid |
| S-PMA | S-phenylmercapturic acid |
| TFL | Tables, Figures, and Listings |
| ULOQ | Upper Limit of Quantification |
| UV | Ultra violet |
| VAS | Visual Analogue Scale |
| WHO | World Health Organisation |
| YG1024+S9 | Ames Mutagenicity Test |

The following special terms are used in this SAP:

| | |
|---|---|
| Baseline period | 06:30 AM at Day -2 until 06:29 AM of Day 1. |
| Conventional cigarette (CC) | The term 'conventional cigarette' refers to commercially available cigarettes (manufactured) and excludes cigars, pipes, bidis, and other nicotine-containing products.. |
| Day of Discharge | Day 6 |
| Enrolment | On Day -3 for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily met and the subject is willing and ready to use CHTP 1.0. |
| Exposure period | 06:30 AM of Day 1 until 11:00 PM of Day 5 |
| Randomization | Allocation of 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 prior to the first product use. |
| Admission period | Day -3 until start baseline period. |
| Safety follow-up | After the time of Discharge, a 7-day safety follow-up will be done for the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site. |
| Screening failure | Subjects who are not enrolled will be considered a screening failure and will be replaced by other subjects. |
| Carbon Heated Tobacco Product 1.0 (CHTP 1.0) | CHTP 1.0 is a non-menthol tobacco stick which is comparable in shape and form, and is used in a similar manner to a conventional cigarette. |

# 5 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Primary Objective and Endpoints

1. To demonstrate the reduction of biomarkers of exposure (BoExp) to selected HPHCs in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

   Related Endpoints (Day 5):

   BoExp to HPHCs in urine (expressed as concentration adjusted for creatinine in 24-hour urine):

   BoExp to 1,3-butadiene: monohydroxybutenylmercapturic acid (MHBMA).

   BoExp to acrolein: 3-hydroxypropylmercapturic acid (3-HPMA).

   BoExp to benzene: S-phenylmercapturic acid (S-PMA).

   BoExp to carbon monoxide (CO):

   Carboxyhemoglobin (COHb) in blood (expressed as % of saturation of hemoglobin).

## 5.2 Secondary Objectives and Endpoints

1. To determine the reduction of additional BoExp to HPHCs in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

   Related Endpoints (Day 5):
   BoExp to CO:

   CO in exhaled breath (expressed as ppm).

   BoExp to HPHCs in urine (expressed as quantity excreted and concentration adjusted to creatinine):

   BoExp to 1,3-butadiene: MHBMA (expressed only as quantity excreted) .

   BoExp to acrolein: 3-HPMA (expressed only as quantity excreted).

   BoExp to benzene: S-PMA (expressed only as quantity excreted).

   BoExp to pyrene: Total 1-hydroxypyrene (Total 1-OHP).

   BoExp to N-nitrosonornicotine: Total N-nitrosonornicotine (Total NNN).

   BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP).

BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA).

BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA).

BoExp to o-toluidine: o-toluidine (o-tol).

BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).

BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA).

BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene.

BoExp to crotonaldehyde: 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA).

BoExp to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butadone (NNK): Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL).

2. To describe the levels of selected BoExp over the Exposure Period in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

Related Endpoints (Day 1 to Day 5):
BoExp to CO:

CO in exhaled breath (expressed as ppm).

COHb in blood (expressed as % of saturation of hemoglobin).

BoExp to various HPHCs in urine (expressed as quantity excreted and concentration adjusted to creatinine):

MHBMA

3-HPMA

S-PMA

Total 1-OHP.

Total NNN.

4-ABP.

1-NA.

2-NA.

o-tol.

CEMA.

HEMA.

3-hydroxybenzo(a)pyrene.

3-HMPMA.

Total NNAL.

3. To determine the levels of nicotine on Day 5 in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC and to describe their levels over the Exposure Period.

Related Endpoint (Day 1 to Day 5):
BoExp to nicotine:

Nicotine equivalents (NEQ): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide in 24 hour urine (expressed in quantity excreted and concentration adjusted to creatinine).

Nicotine and cotinine in plasma.

4. To describe the changes in CYP1A2 enzymatic activity in smokers switching from CC to CHTP 1.0, and in smokers continuing to use CC.

Related Endpoint (Day 5):
Molar metabolic ratio of paraxanthine/caffeine (CAF) in plasma.

5. To describe the daily CHTP 1.0/CC consumption over the Exposure Period in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

Related Endpoint (Day 1 to Day 5):
Number of CHTP 1.0 and CC used each day for each subject.

6. To monitor the safety profile during the study:

Related Endpoints:
Incidence of adverse events (AEs)/ serious adverse events (SAEs).

Incidence of CHTP 1.0 malfunctions and misuse, including the incidence of heat source drop off.

Respiratory symptoms: cough assessment by visual analogue scale (VAS). Likert scales, and one open question.

Vital signs.

Spirometry.

Electrocardiogram (ECG).

Clinical chemistry, hematology, and urine analysis safety panel.

Physical examination.

Concomitant medications.

## 5.3 Exploratory Objectives and Endpoints

1. To describe the following parameters in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

   Related Endpoints:
   Excretion of mutagenic material in urine: Ames mutagenicity test (YG1024+S9) on Day 5 in 24-hour urine.

   Subjective effects of smoking:

   Questionnaire of smoking urges (brief version): Day 1 to Day 5.

   Minnesota nicotine withdrawal scale, revised version: Day 1 to Day 5.

   Cytochrome P450 2A6 (CYP2A6) enzymatic activity: the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine: Day 6.

2. To evaluate the relationship between the levels of BoExp and NEQ in smokers switching from CC to CHTP 1.0, and in smokers continuing to use CC.

   Related Endpoint (Day 5):

   NEQ and BoExp in 24-hour urine.

3. To describe the following parameters over the course of the study in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

Related Endpoints:

Product evaluation: modified cigarette evaluation questionnaire (MCEQ) (Day 1 to Day 5).

Puffing topography (Day -2, Day 1, and Day 4) and the Human Puffing Topography (HPT) questionnaire.

Plug and diffuser analysis: smoke nicotine in plug and diffuser (Day 4).

## 5.4 Study Hypotheses And Evaluation Criteria

### 5.4.1 Hypotheses

The hypotheses to be tested are that the geometric means of the BoExp levels for CHTP 1.0 are lower relative to CC on Day 5.

### 5.4.2 Evaluation Criteria

The study is designed to be able to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in the CHTP 1.0 arm compared to the CC arm at the end of Exposure Period, using a one sided test with 2.5% type I error probability.

# 6 INVESTIGATIONAL PLAN

## 6.1 Study Design

This is a randomized, controlled, open-label, 2-arm, parallel group, single-center study with a stratified randomization by sex and average daily CC consumption over the last 6 weeks prior to admission as self-reported (smokers smoking 10 to 19 CC/day and smokers smoking > 19 CC/day) (**Figure 1 "Study Flowchart"**).

This is an *ad libitum* smoking study. In general, smoking during confinement will be allowed between 06:30 AM and 11:00 PM. During the confinement period, compliance to product/regimen allocation (exclusive use of CHTP 1.0 and CC in the respective arms) will be ensured by strict product distribution..

**1) The Screening Period covers 6 weeks prior to Admission to the clinic (from Day -45 until Admission on Day -3):**

A demonstration of CHTP 1.0 (without product use) will be done by the site collaborators during the Screening Visit. At Screening, spirometry needs to be done at least 1 hour after having stopped smoking. Use of any tobacco/nicotine containing product other than CC will not be allowed after the Screening Visit.

**2) The Admission Day (from Admission on Day -3 until 06:29 AM of Day -2):**

Subjects will be in a confinement setting for 9 days from Day -3 onwards. On Day -3 (Admission), after all inclusion/exclusion criteria are checked, eligible subjects will be enrolled and then perform a product test using up to 5 CHTPs 1.0. After the product test, subjects not ready to use the CHTP 1.0 will be discontinued. All subjects that are not enrolled are considered as screen failures. Smoking will be allowed until 11.00 PM at Admission.

**3) The Baseline Period (from Day -2, 06:30 AM until Day 1, 06:29 AM):**

All subjects will continue smoking their single preferred brand of CC *ad libitum*. Twenty four-urine collection for Day -2 will start in the morning of Day -2 ending in the morning of Day -1. Twenty four-urine collection for Day -1 will start in the morning of Day -1 ending in the morning of the Day 1. During Day -1, spirometry and CYP2A6 blood sampling have to be done prior to smoking.

On Day -1, subjects will be randomized to 1 of the 2 study arms in a 1:1 ratio using a stratified randomization:

CHTP 1.0 arm: ~40 subjects, *ad libitum* use of CHTP 1.0.

CC arm: ~40 subjects, *ad libitum* use of CC.

Subjects will be informed of their randomized study arm by the site collaborators on Day 1 prior to 06:30 AM (the start of the Exposure Period).

**4) The Exposure Period (from Day 1, 06:30 AM until Day 5, 11:00 PM):**

The Exposure Period will consist of 5 days of *ad libitum* use of the assigned product (CHTP 1.0 or CC, exclusively) between 06:30 AM and 11:00 PM.

Subjects in the CC and CHTP 1.0 arms who are willing to attempt quitting during the study will be encouraged to do so and will be referred to a smoking cessation aid service. The subjects will not be discontinued from the study, will come to all scheduled visits for assessments, and his/her financial compensation will not be affected.

Use of any tobacco/nicotine containing product other than the assigned product will not be allowed throughout the Exposure Period and may, at the discretion of the Investigator, result in the subject's discontinuation from the study.

Twenty four-hour urine will be collected from Day 1 to Day 5 on site to measure BoExp. On Day 1, product use must not start prior to the end of urine collection of Day -1. The end of the 24-h urine collection period for Day 5 will end in the morning of Day 6 prior to Discharge.

**5) The Day of Discharge (Day 6) (from Day 5, 11:01 PM to Discharge):**

Procedures of Discharge including but not limited to laboratory parameters will be conducted to discharge the subject from the clinic. Use of CC will be allowed on Day 6 but only after twenty four-hour urine collection is completed, and spirometry and CYP2A6 blood sampling have been performed.

**6) The Safety Follow-up Period (from Discharge on Day 6 to Day 13):**

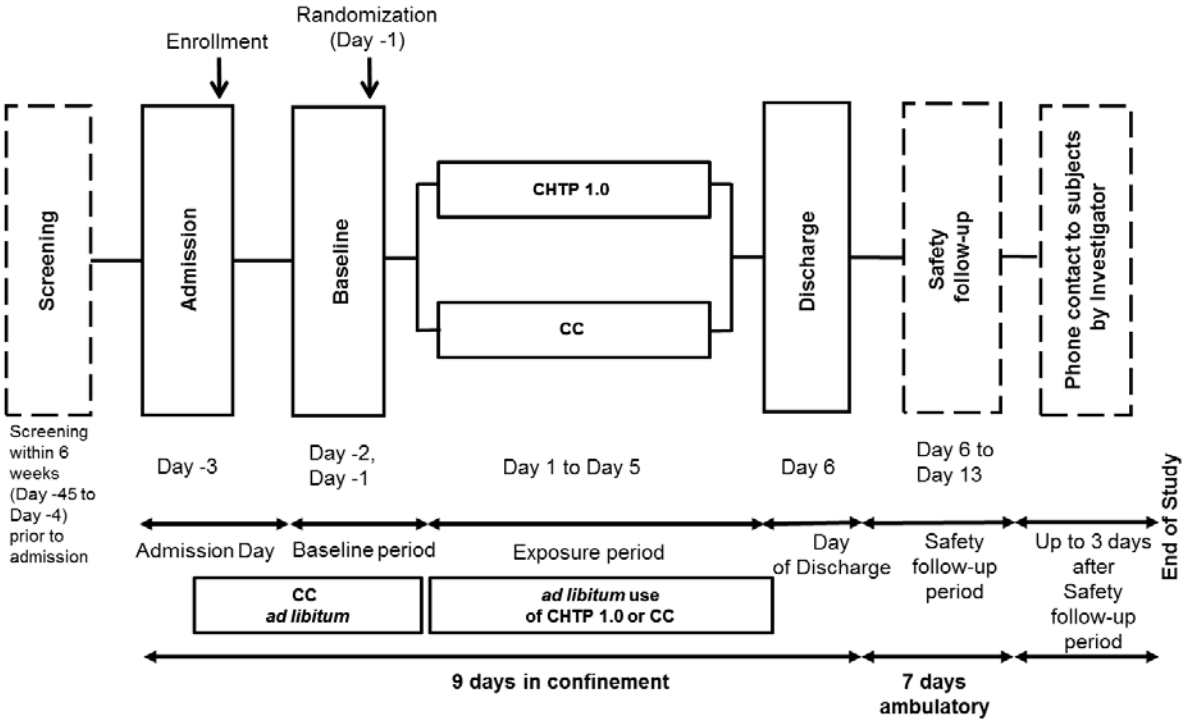
After Discharge, the subject will enter a 7-day Safety Follow up Period during which the follow-up of ongoing AEs/SAEs will be done by the study site. All AEs will be followed-up until resolved, stabilized (*i.e.*, no worsening of the event), or a plausible explanation for the event has been found until the end of the Safety Follow-up Period. Within 3 days after the end of the Safety Follow-up Period the investigator will attempt to contact the subjects by phone to check for if all AEs/SAEs potentially occurring during the Safety Follow-up period are fully reported. At the end of the Safety Follow-up Period, all ongoing AEs will be documented as "ongoing" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner for follow up on ongoing AEs.

The end of the study for a subject is defined as Discharge on Day 6 or the date of early termination of the subject plus the 7 days for the Safety Follow-up Period plus up to 3 days to ensure that all AEs/SAEs potentially occurring during the Safety Follow-up period are fully reported.

If the investigator can reach the subject by phone within 3 days after the end of the Safety Follow-up Period, the date of this phone call with the subject will be recorded as the date of the end of the study of the subject. If the investigator cannot reach the subject by phone within 3 days after the end of the Safety Follow-up Period, the date of the last contact (e.g., last visit of the subject, last phone call with the subject) will be recorded as the date of the end of the study of the subject.

The EOS of the entire study is the end of the Safety Follow-up Period plus up to 3 days of the last subject.

**Figure 1 Study Flowchart**




**Abbreviations**: CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CC = Conventional cigarettes

## 6.2 Selection of Study Population

### 6.2.1 Inclusion Criteria

The inclusion criteria are:

1. Subject has signed the ICF and is able to understand the information provided in the ICF
2. Subject is aged ≥ 21 years.
3. Subject is of Caucasian origin.
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, medical history, and X-ray).
5. Subject smokes at least 10 commercially available non-menthol CCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/CC, as labelled on the cigarette package, at least for the last 6 weeks prior to Admission, based on self-reporting.
6. The subject has been smoking at least for the last 3 years. The smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).

7. The subject does not plan to quit smoking in the next 3 months.
8. The subject is ready to comply with the study protocol (e.g., to use CHTP 1.0).

### 6.2.2 Exclusion Criteria

The exclusion criteria are:

1. As per the Investigator (or designee) judgment, the subject cannot participate in the study for any reason (e.g., medical, psychiatric and/or social reason).
2. The subject is legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, in a social or sanitary establishment, prisoner or involuntarily incarcerated).
3. Clinically relevant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric or cardiovascular disorders or any other conditions that in the opinion of the investigators would jeopardize the safety of the participant or affect the validity of the study results.
4. Abnormal findings on physical examination, in the medical history, or in clinical laboratory results deemed clinically relevant by investigators (as per the common terminology criteria for adverse events [CTCAE]).
5. The subject has ($FEV_1$/FVC) < 0.7 and FEV1 < 80% of the predicted value at post-bronchodilator spirometry.
6. 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).
7. The subject has a body mass index (BMI) < 18.5 or ≥ 32 kg/$m^2$.
8. As per the Investigator's or designee'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.
9. The subject has used nicotine-containing products other than commercially available CC (either tobacco-based products or nicotine replacement therapies), as well as electronic cigarettes and similar devices after the Screening Visit, i.e., within 6 weeks prior to admission.
10. The subject has received medication (prescription or over-the-counter) in Table 2 of the protocol (except for vitamins) within 14 days or within 5 half-lives of the drug (whichever is longer) prior to Admission (Day -3) which has an impact on CYP1A2 or CYP2A6 activity.
11. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject 's participation in the study.
13. The subject has a positive urine drug test.
14. The subject has positive serology test for human immunodeficiency virus (HIV)1/2, hepatitis B or hepatitis C.
15. The subject has donated or received whole blood or blood products within 3 months prior to Admission.

16. The subject is a current or former employee of the tobacco industry or their first-degree relatives (parent, sibling, child).
17. The subject is an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent, sibling and child).
18. The subject has participated in a clinical study within 3 months prior to the Screening Visit.
19. The subject has been previously screened in this study.
20. For women only: Subject is pregnant (does have positive pregnancy tests at the Screening and at Admission) or is breast feeding.
21. For women 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 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 plus up to 3 days. Hysterectomy, tubal ligation, bilateral oophorectomy or post-menopausal status are reasons for not needing to use birth control. Post-menopausal status is defined as women who have not experienced menses for greater than 12 months. If a woman claims she's post-menopausal, but has had her menses within 12 months, a follicle stimulating hormone test must be performed and must be within acceptable limits.

## 6.3 Product Allocation and Blinding

### 6.3.1 Methods of Assigning Subjects to Product Arms

When all the eligibility criteria have been met, the subject will be enrolled on Day -3. Randomization will be done through [redacted] on Day -1 at any time during the day. Subjects will be randomized to one of the 2 study arms: CHTP 1.0:CC in a 1:1 ratio. Subjects will be informed of their randomized study arm in the morning of Day 1, prior to 06:30 AM (the start of the Exposure Period).

Stratified randomization will be conducted by sex and by average daily CC consumption over the last 6 weeks prior to Admission as self-reported (smokers smoking 10 to 19 CC/day and smokers smoking > 19 CC/day). In each arm, each sex and each of the smoking strata should have a quota applied to ensure they represent at least 40% of the population.

### 6.3.2 Blinding

This is an open-label study; therefore the subjects and Investigators or designees will be unblinded to the subject's arm. However, there will be a limited degree of blinding in the data review and data analysis process. In particular, PMI and contract research organization (CRO) personnel will be blinded to the randomized arm as summarized in Table 1.

**Table 1: Blinding Scheme**

| Blinded Study Personnel | End of Blinding Period |
|---|---|
| PMI and CRO study statisticians | After the SAP finalization or database lock[1], whichever comes last. |
| PMI study data managers | After the finalization of PMI blind database review[2]. |
| 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 arm 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 study arms will be ensured by strict distribution of the products (stick by stick) and collection of the CC butts and CHTP 1.0 after each use. Distribution and return of these products will be documented in appropriate logs.

## 7 DERIVED AND COMPUTED VARIABLES

Mean change from baseline (baseline is defined in Section 12.1.4 “Definitions for Statistical Data Analysis”) is the mean of all individual subjects’ change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject’s baseline value from the value at the timepoint.

Mean percent change from baseline is the mean of all individual subjects’ percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual subject’s baseline value from the value at the desired timepoint and then

dividing this calculated value by the individual subject's baseline value and multiplying by 100.

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

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

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

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

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

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

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

## 7.1 Biomarkers

### 7.1.1 Biomarkers of Exposure

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

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

where the [ ] indicated concentrations measured from the same 24 hour urine collection.

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

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

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

### 7.1.2 Nicotine Equivalents

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

NEQ [g] = (free nicotine$_c$[µmol/L] + nicotine-glucuronide$_c$ [µmol/L]
+ free cotinine$_c$ [µmol/L] + cotinine-glucuronide$_c$ [µmol/L]
+ free *trans*-3'-hydroxycotinine$_c$ [µmol/L]
+ *trans*-3'-ydroxycotinine-glucuronide$_c$ [µmol/L])
*162.2[µg/µmol]*urine volume (L) / 1000 [µg/mg]

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

The conversion factors will be applied as follows:

| | |
|---|---|
| Free nicotine | The molecular weight is 162.232 g/mol (**Chemical Information Specialized Information Services RN:54-11-5**). Therefore to convert nicotine from ng/mL to nmol/L, the result in ng/mL is multiplied by 6.164. |
| Nicotine glucuronide | The molecular weight is 338.356 g/mol (**Chemical Information Specialized Information Services RN:152306-59-7**). Therefore to convert nicotine from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.955. |
| Cotinine | The molecular weight is 176.218 g/mol (**Chemical Information Specialized Information Services RN:486-56-6**). Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 5.675. |
| Cotinine-glucuronide | The molecular weight is 352.341 g/mol (**Chemical Information Specialized Information Services RN:139427-57-9**). Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 2.838. |
| Trans-3'hydroxycotinine | The molecular weight is 192.217 g/mol (**Chemical Information Specialized Information Services RN:34834-67-8**). Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202. |
| Trans-3'hydroxycotinine-glucuronide | The molecular weight is 368.34 g/mol (**Chemical Information Specialized Information Services RN:132929-88-5**). Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.715. |

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

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

### 7.1.3 CYP1A2

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

The conversion factor will be applied as follows:

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

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

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

### 7.1.4 CYP2A6

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

The conversion factor will be applied as follows:

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

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

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

## 7.2 Questionnaires

All used questionnaires are available as a validated questionnaire in Polish.

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

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

**Table 2** 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 2: 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 (up to ½ pack)<br>▪ 11 to 20 (a little more than ½ pack, up to a full pack)<br>▪ 21 to 30 (a little more than a pack, up to 1½ packs)<br>▪ 31 or more (more than 1½ packs) | 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 |

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

The QSU-brief (**Cox et al. 2001**) is a self-reported questionnaire completed daily from Day -2 to Day 5 between 08:00 PM and 11:00 PM.

The QSU-brief consists of 10 items as presented in **Table 3**.

| Table 3: 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 also be derived (**Cox et al. 2001**). Each factor is a subset that includes 5 of the 10 questions as defined in **Table 3.** 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.

### 7.2.3 Modified Cigarette Evaluation Questionnaire

The MCEQ (**Cappelleri et al. 2007)** will be completed by the subject him/herself daily from Day -2 to Day 5 between 08:00 PM and 11:00 PM, to assess the degree to which subjects experience the reinforcing effects of smoking.

The MCEQ consists of 12 items as presented in **Table 4**.

**Table 4: 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.

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

The MNWS (**Hughes and Hatsukami 2008**) is a 24 hour recall that will be completed by the subject him/herself daily on Day -1 to Day 6 prior to product use to reflect the previous days experience. Therefore although it is collected on Days -1 to 6 it will be reported as Days -2 to 5.

The self-reported part of the MNWS, that was administered in this study consists of the following 15 items which are rated on a scale of 0 to 4 (see **Table 5**). Higher scores indicate greater intensity on that scale.

The total scores will be derived by calculating the average of all the non-missing data per Total Score as shown in **Table 5**. The first total score consists of the first 9 items, the second total score is based on 6 extra items which are thought to have an impact on withdrawal but have not been validated. If more than 50% of the items are missing then the total score will be set to missing.

| Table 5: Minnesota Nicotine Withdrawal Scale (Revised Edition) Questionnaire Scores | | |
|---|---|---|
| | **Question** | **Total Score** |
| 1 | Angry, irritable, frustrated. | 1 and 2 |
| 2 | Anxious, nervous. | 1 and 2 |
| 3 | Depressed mood, sad. | 1 and 2 |
| 4 | Desire or craving to smoke. | 1 and 2 |
| 5 | Difficulty concentrating. | 1 and 2 |
| 6 | Increased appetite, hungry, weight gain. | 1 and 2 |
| 7 | Insomnia, sleep problems, awakening at night. | 1 and 2 |
| 8 | Restless. | 1 and 2 |
| 9 | Impatient. | 1 and 2 |
| 10 | Constipation | 2 |
| 11 | Dizziness | 2 |
| 12 | Coughing | 2 |
| 13 | Dreaming or nightmares | 2 |
| 14 | Nausea | 2 |
| 15 | Sore throat | 2 |

### 7.2.5 Human Puffing Topography Questionnaire

A specific subject self-reported questionnaire, used for exploratory purposes, has been developed by PMI to evaluate the impact of the use of the HPT SODIM® device on smoker's puffing experience in terms of ritual disruption. This is a questionnaire with 5 items to be rated on a 5-point scale (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) and an open question for each item in case the subject agrees or strongly agrees (**Table 6**). Subjects will be asked by the Investigator or designee to complete the HPT questionnaire at:

> On Day -2, HPT and HPT questionnaire will be done in all subjects using CC compatible with the HPT SODIM®
>
> On Day 1 and Day 4 in the confinement period, HPT and HPT questionnaire will be done in all subjects in the CHTP and CC arms. Puffing topography with the HPT SODIM® device will not be done in subjects using CC that are incompatible with the HPT SODIM® device (e.g., slim CC).

| Table 6: Human Puffing Topography Questionnaire |
|---|
| **Question** |
| Smoking of the conventional cigarettes or using of the tested products is different with the device. |

**Table 6: Human Puffing Topography Questionnaire**

| Question |
|---|
| You enjoy smoking the conventional cigarettes or using of the tested products with the device as much as without it. |
| The taste of the conventional cigarette or of the tested products is different with the device. |
| The device is easy to use. |
| Your smoking of the conventional cigarettes or your using of the tested products is disturbed by the device. |

### 7.2.6 Cough Assessment

Subjects will be asked to assess the respiratory symptom 'cough' using a VAS, three Likert scale questions, and one open ended question on a daily basis during the confinement period (on Day -1 to Day 6) prior to 11:30 AM or at 06:29 AM ± 1 hour on Day 6.

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

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

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

| Table 7 Cough Assessment Likert Scales | |
|---|---|
| **Question** | **Likert Scale** |
| | 1 = a moderate amount of sputum;<br>2 = a larger amount of sputum;<br>3 = a very large amount of sputum. |
| Open question: Are there any other important observations that you would like to share with us about your coughing? | |

## 7.3 Human Puffing Topography Assessment

The HPT SODIM® device measures and records the flow and other per-puff parameters listed below (Table 8). From the per-puff parameters, the per-cigarette parameters shown below will be derived (representing average values or totals per cigarette (Table 9)). Prior to calculation of the per-cigarette parameters, the topography data will be processed through analysis software. Only data that are able to be processed by the software will contribute to the per-cigarette parameters and will be part of the study database.

| Table 8:HPT- Per-Puff Parameters | | |
|---|---|---|
| **Description** | **Variable** | **Unit** |
| Puff number | Ni | |
| Puff volume | Vi | mL |
| Puff duration | Di | S |
| Average flow [Vi/Di] | Qmi | mL/s |
| Peak flow | Qci | mL/s |
| Inter puff interval | Ii | S |
| Sum of Ii and Di | Dfi | S |
| Work [INT Pmi*FinalFlow*dt] | Wi | mJ |
| Average pressure drop | Pmi | mmWG |
| Peak pressure drop | Pci | mmWG |
| Average resistance [Pmi/Qmi] | Rmi | mmWG/mL/s |
| Peak resistance [Pci/Qci] | Rci | mmWG/mL/s |
| Number of peak(s) in the puff | Pn | |

| Table 9:HPT - Per-CHTP / Cigarette Parameters | | | |
|---|---|---|---|
| **Description** | **Variable** | **Formula** | **Unit** |
| Total number of puffs | NPC | Σ Ni | |
| Total puff volume | TVOL | Σ Vi | mL |
| Average puff volume | AvgVi | Σ Vi / NPC, i=1 ... NPC | mL |

| Table 9:HPT - Per-CHTP / Cigarette Parameters | | | |
|---|---|---|---|
| **Description** | **Variable** | **Formula** | **Unit** |
| Average puff duration | AvgDi | Σ Di / NPC, i=1 ... NPC | s |
| Total puff duration | TDi | Σ Di | s |
| Average flow | AvgQmi | Σ Qmi / NPC, i=1 … NPC | mL/s |
| Peak flow | AvgQci | Σ Qci / NPC, i=1 … NPC | mL/s |
| Total inter puff interval | TIi | Σ Ii | s |
| Average inter puff interval | AvgIi | Σ Qci / NPC, i=1 … NPC | s |
| Total smoking duration | TDFi | Σ DFi | s |
| Total work | TWi | Σ Wi | mJ |
| Average work | AvgWi | Σ Wi / NPC, i=1 … NPC | mJ |
| Average pressure drop | AvgPmi | Σ Pmi / NPC, i=1 … NPC | mmWg |
| Average peak pressure drop | AvgPci | Σ Pci / NPC, i=1 … NPC | mmWg |
| Puffing intensity | SMINT | TVOL/TDFi | mL/s |
| Puffing time index | PTI | (100*TDi)/TDFi | % |
| Puff frequency | PFeq | NPC/(TDFi/60) | $Min^{-1}$ |
| Average puff volume per peak | AvgVpn | Σ (Vi/Pn) / NPC, i=1 … NPC | mL/s |
| Average puff duration per peak | AvgDpn | Σ (Di/Pn) / NPC, i=1 … NPC | s |

## 7.4 Categorical Variables

The categorical variables used in this study are shown below (**Table 10**).

| Table 10: Categorical Variables Definitions | | |
|---|---|---|
| **Variable** | **Categories** | |
| BMI ($kg/m^2$) | Underweight: | < 18.5 |
| | Normal range: | ≥ 18.5 and < 25.0 |
| | Overweight: | ≥ 25.0 and < 30.0 |
| | Obese: | ≥ 30.0 |
| FTND total score | Mild: | 0 – 3 |
| | Moderate: | 4 – 6 |
| | Severe: | 7 – 10 |
| ISO tar yields | 1 – 5 mg | |
| | 6 – 8 mg | |

**Table 10: Categorical Variables Definitions**

| Variable | Categories |
|---|---|
| | 8– 10 mg |
| | > 10 mg |
| Nicotine level | <= 0.6 mg |
| | > 0.6 to <= 1 mg |
| Daily CC consumption over the last 4 weeks as reported at Screening (per day). | 10-19 |
| | >19 |
| CO breath test level (ppm) | ≤ 10 |
| | > 10 |
| COHb level | ≤ 2% |
| | > 2% |
| Adverse event severity | Mild |
| | Moderate |
| | Severe |
| Adverse event relationship | Related |
| | Not related |
| Adverse event expectedness | No |
| | Yes |
| Action taken with study product due to adverse event | Product use interrupted |
| | Product use withdrawn |
| | Product use reduced |
| | None |
| 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 hospitalization |
| | Results in disability/incapacity |
| | Congenital anomaly/birth defect |
| | Other medically important event |

# 8 SAMPLE SIZE JUSTIFICATION

The following discussion addresses the ability to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.0 arm compared to the CC arm after 5 days of exposure, with 80 randomized subjects in a 1:1 ratio (40 in CHTP 1.0 arm and 40 in CC arm) and a one sided test with 2.5% type I error probability.

**Table 11** describes the expected coefficients of variation (CV) and mean ratios (MR) between CHTP 1.0 and the control arm based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study that investigated exposure to selected smoke constituents in smokers switching from CC to smoking article cigarettes for 5 days, the YVD-CS01-EU study (ClinicalTrials.gov: ID: NCT00812279) sponsored by PMI.

**Table 11: Coefficients of Variation (YVD-CS01-EU study)**

| | **CHTP 1.0/CC MR (CV)** |
|---|---|
| COHb | 0.40 (0.32) |
| 3-HPMA | 0.30 (0.50) |
| MHBMA | 0.15 (0.70) |
| S-PMA | 0.20 (0.70) |

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = Conventional cigarettes; COHb = Carboxyhemoglobin; CV = Coefficients of variation; MHBMA = Monohydroxybutenyl mercapyuric acid; MR = Mean ratios; S-PMA = S-phenylmercapturic acid; CHTP 1.0 = Carbon Heated Tobacco Product 1.0

The power to detect a reduction was computed.

**Table 12** describes the expected power to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.0 arm compared to the CC arm after 5 days of exposure, with a one sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU.

**Table 12: Expected Power (YVD-CS01-EU Studies Assumptions)**

| | **Reduction** | | | | | |
|---|---|---|---|---|---|---|
| **Assumptions** | **50%** | **51%** | **52%** | **53%** | **54%** | **55%** |
| YVD-CS01-EU | 88% | 82% | 73% | 62% | 49% | 35% |

The test-wise powers to detect a reduction of 50% or more in CHTP 1.0 arm compared to the CC arm after 5 days of exposure using the assumptions from YVD-CS01-EU are described in **Table 13**.

| Table 13: Test-Wise Power (YVD-CS01-EU study assumptions) | |
|---|---|
| **Parameter** | **Test-wise power** |
| COHb | 88% |
| 3-HPMA | >99% |
| MHBMA | >99% |
| S-PMA | >99% |

Given the above calculation, the sample size was considered sufficient to have more than 80% power to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.0 arm compared to the CC arm.

# 9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

Shift tables for safety endpoints will not be produced for this study. The relevant information provided in the listings is considered to be sufficient. Reason for change: the duration of the study would not allow for seeing trends in shifts tables.

Statistical analysis for the QSU-brief questionnaire data, MNWS questionnaire data and the MCEQ questionnaire data will be performed including interaction terms for product and time point to enable least square means to be calculated at each time point in order to explore the pattern of the CHTP 1.0 effect over time. The main comparison between products will be the comparison over all of the time points. Reason for change: this analysis would capture the daily evolution of perception of the product and the adaptation process taking into account the subjects' repeated measurements.

The second exploratory objective ("To evaluate the relationship between the levels of BoExp in 24-hour urine on Day 5 and NEQ in smokers switching from CC to CHTP 1.0, and in smokers continuing smoking CC") will be reported in a separate report. Reason for change: this analysis would be supportive only of analyses not accounting for NEQ difference between exposure groups.

A sensitivity analysis using the PP Population will be performed for every non-safety objective. This will be done if the FAS is not equal to the PP Population. If this is the case, then the table numbering as presented below will be adapted so that a ".1" is added to the FAS table and a ".2" is added to the PP table. Reason for change: the analysis on PP population would allow interpretability with studies in which PP population would be the primary set for analysis. The protocol was planning this analysis to be carried out only if

the PP population would differ from the FAS by more than 20%. It was decided to present the analyses for both FAS and PP regardless of difference in size between the two populations. .

The term “adjusted to creatinine” has been replaced by “adjusted for creatinine” in all relevant endpoints and analyses. Reason for change: the term was considered more gramatically correct than the original one from the protocol.

The descriptive statistics of the biomarkers of the primary endpoints will also be calculated per stratification factor. Reason for change: the protocol specified that primary endpoint analyses would be done by stratification factor, and this clarifies that descriptive statistics will also be presented by stratification factor.

An analysis of plasma nicotine and cotinine and NEQ will be done covering the exposure period. Reason for change: this analysis would serve to supplement the measure of difference of exposure between CC and CHTP arms over the entire exposure period.

New parameters were added to Human Puffing Topography Assessment (Number of peak(s) in the puff, Average puff volume per peak, Average puff duration per peak) in Tables 8 and 9. Reason for change: These additional parameters would improve the assesment of topography.

# 10 ANALYSIS POPULATIONS

The main population for non-safety analysis will be the full analysis set (FAS). In addition, a sensitivity analysis using the PP Population will be performed for every non-safety objective. This will be done if the FAS is not equal to the PP Population.

Safety data will be analyzed using the Safety Population.

## 10.1 Screened Population

The screened population consists of all subjects who gave informed consent.

## 10.2 Randomized Population

The randomized population consists of all subjects who were randomized.

## 10.3 Full Analysis Set

The FAS consists of all the randomized subjects who had at least one post-randomization product use experience and have at least one valid non-safety assessment.

## 10.4 Per Protocol Population

The PP population is a subset of the FAS and includes all randomized subjects who have no major protocol deviations impacting evaluability as defined **Table 14** (see Section **11**"**Protocol Deviations**").

## 10.5 Safety Population

The Safety Population consists of all the subjects who had at least one exposure to CHTP1.0 (product test at Admission Day). Subjects in the Safety Population will be analyzed according to actual exposure.

# 11 PROTOCOL DEVIATIONS

Protocol deviations are defined as deviations from the study procedures, including but not limited to any violation of inclusion/exclusion criteria, assessments not performed or performed outside the scheduled time windows, or use of drugs that are known to affect study endpoints.

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

All deviations will be reviewed and each deviation will be classified as major or minor; all major deviations will be further reviewed to determine whether or not the deviation impacts the evaluability of the results and therefore should result in the subject being excluded from the PP Population.

## 11.1 Major Protocol Deviations

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

The categories for the major deviations may include, but are not limited to the deviations presented in **Table 14**.

**Table 14: Definition of Major Protocol Deviations**

| Category | Description |
|---|---|
| Mis-randomization | An error in the randomization and/or product allocation process including being administered the wrong product according to the randomization schedule. |
| Product compliance | Use of any nicotine or tobacco–containing product other than the assigned product. |
| Protocol violation | A deviation to the inclusion/exclusion criteria. |
| Procedural violation | A deviation in the conduct of a procedure |
| Violation of 24 hour urine collection | Not all urine collected over 24 hours or collection period does not cover 24h +/- 30 min |
| Concomitant medication | Use of drugs which are known to affect CYP2A6 activity. |

Subjects with violations of inclusion criteria 1, 2, 4 and 6, or of exclusion criteria 2 to 4, 10, 16, 19 and 20 will be excluded from the PP Population. Other violations of the inclusion and exclusion criteria will be reviewed for their impact on the evaluability of the primary objectives during the pre-analysis data review meeting (Section 10.4 "Per Protocol Population").

## 11.2 Minor Protocol Deviations

The categories for the minor deviations may include, but are not limited to the deviations presented in **Table 15**.

**Table 15: Definition of Minor Protocol Deviation Categories**

| Category | Description |
|---|---|
| Time deviation (Questionnaires) | Assessments not taken at the correct time or within the allowed time window (see Table 16) |
| Time deviation (Blood draws) | Assessments not taken at the correct time or within the allowed time window (see Table 16) |
| Time deviation (CYP1A2 activity) | Assessments not taken at the correct time or within the allowed time window (see Table 16) |
| Time deviation (CYP2A6 activity) | Assessments not taken at the correct time or within the allowed time window (see Table 16) |
| Time deviation (Assessment of cough) | Assessments not taken at the correct time or within the allowed time window (see Table 16) |
| Time deviation (CO breath test) | Assessments not taken at the correct time or within the allowed time window (see Table 16) |
| Visit window deviation | Assessments not taken at the correct time or within the allowed time window (see Table 16) |

| Table 15: Definition of Minor Protocol Deviation Categories | |
|---|---|
| **Category** | **Description** |
| Time missing | Assessment date or time is missing |
| Procedural violation | A deviation in the conduct of a procedure |
| Assessment missing | Assessment is missing |
| Visit missing | Scheduled visit not done |

## 11.3 Assessment Windows

Smoking of the randomized products should take place within the 06:30 AM and 11:00 PM window.

The assessment windows are shown in **Table 16**.

| Table 16: Assessment Windows | | |
|---|---|---|
| **Assessment** | **Nominal Time point(s)** | **Window** |
| 24 h urine sample | Start (All days)<br>End on the following day (All days) | 06:30 AM ± 1 hour<br>06:29 AM ± 1 hour |
| CYP1A2 activity in plasma | Start (Days -1 and 5) | 6 hours after intake of cup of coffee ± 15 min |
| CYP2A6 activity | Day -1 and Day 6 | Prior to smoking / product use |
| CO breath test | Day -2 to Day 5 | In the evening prior to 09:00PM (approx 08:00 PM ± 1 hour) |
| Assessment of Cough | Day -1 to 5<br><br>Day 6 | To be done prior to product use but not later than 11:30 AM<br>06:29 AM ± 1 hour |
| MNWS questionnaire | Day -1 to 5<br><br>Day 6 | To be done prior to product use but not later than 11:30 AM<br>06:29 AM ± 1 hour |
| QSU-brief questionnaire | Day -2 to 5 | 08:00 PM to 11:00 PM |
| MCEQ questionnaire | Day -2 to 5 | 08:00 PM to 11:00 PM |
| Nicotine and cotinine in plasma | Day -2 to Day 5 | In the evening prior to 09:00PM (approx 08:00 PM ± 1 hour) |

| Table 16: Assessment Windows | | |
|---|---|---|
| **Assessment** | **Nominal Time point(s)** | **Window** |
| COHb blood sampling | Day -2 to Day 5 | In the evening prior to 09:00PM (approx 08:00 PM ± 1 hour) |
| HPT Questionnaire | Day -2, Day 1 and Day 4 | 08:00 PM-11:00 PM |
| HPT Recording | Day -2, Day 1 and Day 4 | for all smoking events when compatible CCs are smoked |

# 12 Planned Statistical Methods

## 12.1 General Considerations

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

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

Safety data will be summarized for the Safety Population.

### 12.1.1 Stratified Presentation

For the analysis and descriptive statistics of the primary study endpoints, the following stratification criteria will be used:

1. Sex (male; female).
2. Average daily CC consumption over the 6 weeks prior to admission as reported on the Admission Day (smokers smoking 10 to 19 CC/day and smokers smoking > 19 CC/day).

### 12.1.2 Subgroup Analyses

No subgroup analyses will be performed in this study.

### 12.1.3 Descriptive Statistics

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic SD, median, first and third quartiles, minimum, maximum, and number; for log-normal data the geometric mean and geometric CV will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will include all subject level data collected unless otherwise specified. Summary statistics and statistical analyses will generally only 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 the Safety Population will be produced by actual exposure. Subjects who tested the product but were discontinued before randomization will be shown in a separate column /table.

The following product labels will be used throughout the TFLs (**Table 17**):

**Table 17: Product Labels**

| Product | Format used in TFLs | Order in TFLs |
|---|---|---|
| Carbon Heated Tobacco Product | CHTP | 1 |
| Conventional cigarettes | CC | 2 |

The following stratification labels (**Table 18**) for the TFLs will be used:

**Table 18: Stratification Labels**

| Stratification Factor | Definition |
|---|---|
| Sex | male<br>female |
| Daily CC consumption (per day) | <10[1]<br>10-19<br>>19 |

[1] Note that due to inclusion criteria for the study there should not be any subjects with daily CC consumption < 10, therefore this category will not be presented unless there is sufficient data for analysis/presentation (see Section **12.1.5.1** "**Insufficient Data for Analysis/Presentation**").

### 12.1.4 Definitions for Statistical Data Analysis

The following definitions (**Table 19**) for statistical analyses/presentations will be used:

**Table 19: Definition of terms for the statistical analysis**

| Term | Definition |
|---|---|
| Baseline Value | The last valid assessment prior to 06:30 AM on Day 1 |

For 24-hour urine collections, the collection sample will be labelled by the day in which the collection started. As an example if the 24-hour urine sample is collected from Day 5 to Day 6, it will be analyzed and reported as the Day 5 sample.

### 12.1.5 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 **7.2** "**Questionnaires**".

In general, values below the Lower Limit of Quantification (LLOQ) will be imputed using LLOQ/2. For values above the Upper Limit of Quantification (ULOQ) i.e., preceded by a ">", for example ">xx", the numerical xx will be used for calculation and reporting in summary tables. The number of values below LLOQ or above ULOQ will be presented in each summary table.

12.1.5.1 Insufficient Data for Analysis/Presentation

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

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

### 12.1.6 Handling of Unplanned Data

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

### 12.1.7 Multiple Comparisons / Multiplicity

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

The primary endpoints will be tested using a multiple testing procedure (**EMEA Points to consider on multiplicity issues in clinical trials**) to preserve the overall alpha level by simultaneously testing the endpoints using a closed procedure with each test performed at a two-sided alpha level of 5%.

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

## 12.2 Disposition of Subjects

The number and percent of subjects will be summarized for the following categories: subjects screened, enrolled subjects, exposed and not randomized, randomized subjects, completed, and discontinued (if applicable discontinued subject that never used their allocated products will be identified).

All subjects who screenfail or discontinue the study will be categorized by their primary reason for screen failure or discontinuation. 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 product, 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 listings 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, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.1 | Summary of Subject Disposition – All Screened Subjects |
| 15.2.1.2.1 | Summary of Reasons for Screen Failure – All Screened Subjects |
| 15.2.1.2.2 | Summary of Reasons for Discontinuations – All Enrolled Subjects |
| 15.2.1.3 | Summary of Protocol Deviations – FAS |
| LISTINGS | |
| 15.3.1.1 | Listing of Inclusion/Exclusion Criteria |
| 15.3.1.8 | Listing of Subject Disposition, Randomization and Assignment to Analysis Sets |
| 15.3.1.11 | Listing of Protocol Deviations |
| 15.3.2.2 | Listing of Subject and Observations Excluded from Efficacy Analysis |
| 16.1.7 | Listing of Randomization Schemes and Codes |

## 12.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population, FAS and PP, and listed for all screened subjects.

The demographic variables age, sex, race, body weight, height and BMI will be summarized by exposure, and by sex and CC consumption. Other baseline characteristics and Current CC brand(s) at Admission will also be included in the table.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – FAS |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS |
| 15.2.1.4.3 | Summary of Demographics and Other Baseline Characteristics – PP |
| LISTINGS | |
| 15.3.1.7 | Listing of Demographics |

### 12.3.1 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 part of the demographics and baseline characteristics (Section 12.3).

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – FAS |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS |
| LISTINGS | |
| 15.3.1.10 | Listing of Fagerström Test for Nicotine Dependence Results |

### 12.3.2 Current Cigarette Brand and Smoking Characteristics

The following smoking characteristics at Admission (Day -2) will be summarized and listed as specified in Section 12.3. ISO tar yields (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 and > 0.6 to ≤ 1 mg), and number of CCs smoked on a daily basis during the previous 6 weeks and since the subject started smoking (continuous and categorized as 10-19 CC/day and >19 CC/day).

Current CC brand(s) smoked by the subject and recorded at Admission (Day -3) will be summarized and listed by product for the FAS. This will include brand name(s) and ISO nicotine, tar, and CO yields. Data at screening will be listed only.

Smoking history, including whether subjects have smoked for at least the last three years, number of years smoked, whether the subject used any nicotine containing products other than commercially available non-menthol CC within 6 weeks prior to admission, and e-cigarette use over the last year will be listed by product at Screening and Admission (Day -2) where applicable. 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, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – FAS |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS |
| 15.2.1.5 | Summary of Current Cigarette Brands – FAS |
| LISTINGS | |
| 15.3.1.2 | Listing of Current Cigarette Brands |
| 15.3.1.3 | Listing of Smoking History |
| 15.3.1.4 | Listing of Advice on Risks of Smoking / Smoking Cessation |
| 15.3.1.5 | Listing of Product Test |

### 12.3.3 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 MedDRA version 18.0 and listed separately by product, System Organ Class (SOC) and Preferred Term (PT) within SOC.

Medical History will be summarized by product, SOC and PT for the FAS.

Concomitant disease is defined as any condition diagnosed at Screening or was ongoing at Screening. Concomitant disease will be coded using MedDRA version 18.0 and listed separately by product, SOC and PT within SOC.

Concomitant disease will be summarized by product, SOC and PT for the FAS.

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, the TFL number refers to the TFL number in the accompanying TFL shell document:

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

### 12.3.4 Other Data

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

- Cotinine urine test
- Urine pregnancy test
- Chest x-ray
- Urine drug screen
- Serology
- Alcohol breath test
- Prior and concomitant medication
- Willingness to use CHTP 1.0
- Willingness and ability to use the products will also be summarized.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| LISTINGS | |
| 15.3.1.5 | Listing of Product Test and Willingness to Use the Product |
| 15.3.1.6 | Listing of Safety Laboratory Entry Criteria |
| 15.3.6.3 | Listing of Prior and Concomitant Medication |

## 12.4 Extent of Exposure (Product Consumption)

Details of the product test and of daily product use will be listed and summarized.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.2.1 | Descriptive Statistics of Use of CHTP Product and CC – Safety Population |
| 15.2.2.2 | Descriptive Statistics of Use of CHTP Product and CC – FAS |
| LISTINGS | |
| 15.3.2.1 | Listing of Product Usage |

## 12.5 Planned Statistical Analyses

Markedly non-lognormally distributed BoExp data will be transformed or analyzed by appropriate non-parametric methods with bootstrapping using the SAS procedure PROC SURVEYSELECT. The seed to be used in any analysis will be contained in the SAS output and will be different for each analysis.

For all statistical analysis data from all arms will be included in all models.

### 12.5.1 Primary Analyses

12.5.1.1 COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection

COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA will be summarized as detailed in Section **12.1.3** "**Descriptive Statistics**". In addition, the quantity excreted over 24 hours for each biomarkers of exposure will be presented.

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

The values and percent changes from baseline in the concentration adjusted for creatinine will be listed and summarized along with the COHb concentrations and percent changes from baseline. In addition line graphs will be produced for means (and 95% CI) over all timepoints.

The transformed data will be analyzed by means of a generalized linear model using product arm as covariate adjusting for the following stratification parameters: sex and average cigarette consumption over the previous 6 weeks prior to Admission, and log-transformed baseline value of endpoint.

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

The SAS code to be used is shown below:

```
Proc mixed data=_data_;
Class product sex cigarette_cons;
Model log (Day 5) = log (baseline) sex cigarette_cons  product;
Lsmean product / pdiff =control('CC') alpha=0.05 cl;
Run;
```

The least squares (LS) means and estimate of the difference along with it's 95% CI will be back-transformed before presenting in the tables. The geometric LS means for each product along with the reduction (i.e: 100% - ratio of CHTP : CC) and 95% CI will be presented in the tables.

In addition line graphs will be produced for product geometric means (and 95% CI) over all timepoints for COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.3.1 | Analysis of Biomarkers of Exposure for the Primary Objectives – FAS |
| 15.2.3.2 | Analysis of Urinary Quantity Excreted of MHBMA, 3-HPMA and S-PMA over 24 hours on Day 5 – FAS |
| 15.2.3.3 | Descriptive Statistics of Blood COHb (%) – FAS |
| 15.2.3.3.1 | Descriptive Statistics of Blood COHb (%) by Sex – FAS |
| 15.2.3.3.2 | Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – FAS |

| TFL number | Title |
|---|---|
| 15.2.3.4 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) – FAS |
| 15.2.3.4.1 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS |
| 15.2.3.4.2 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS |
| 15.2.3.5 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) – FAS |
| 15.2.3.5.1 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS |
| 15.2.3.5.2 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS |
| 15.2.3.6 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) – FAS |
| 15.2.3.6.1 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS |
| 15.2.3.6.2 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS |
| FIGURES | |
| 15.1.1.1 | Blood COHb (%) Geometric Mean and 95% CI– FAS |
| 15.1.1.2 | MHBMA Geometric Mean Urinary Concentration Adjusted for Creatinine (units) Mean and 95% CI – FAS |
| 15.1.1.3 | 3-HPMA Geometric Mean Urinary Concentration Adjusted for Creatinine (units) Mean and 95% CI– FAS |
| 15.1.1.4 | S-PMA Geometric Mean Urinary Concentration Adjusted for Creatinine (units) Mean and 95% CI– FAS |
| LISTINGS | |
| 15.3.3.1 | Listing of Biomarkers of Exposure and Sampling / Collection Times |

The listing of the urinary biomarkers will include the concentration, the percent change in the concentration, the concentration adjusted for creatinine, the percent change in the concentration adjusted for creatinine, the volume of urine in the 24 hour collection, the quantity excreted over 24 hours and the percent change in quantity excreted over 24 hours.

The listing of the COHb data will include the concentration, the percent change in the concentration, and a flag for whether a subject's COHb is <2%.

12.5.1.2 Confirmatory Analysis

The hypothesis to be tested for each of the biomarkers of exposure of the primary objectives is that the geometric mean level on Day 5 of the biomarker for CHTP 1.0 is lower relative to CC.

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

Null hypothesis ($H_0$): $m1 \geq m2$

Alternative hypothesis ($H_1$): $m1 < m2$

Where m1 and m2 are the geometric means of the biomarker levels on Day 5 for CHTP 1.0 and CC respectively.

The SAS code will be the same as described in Section **12.5.1.1** "**COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection**".

### 12.5.2 Secondary Analyses

12.5.2.1 Biomarkers of Exposure

12.5.2.1.1 Exhaled CO

CO in exhaled breath (expressed as ppm), will be measured using the Micro+™ Smokerlyzer® or similar device, conducted on Day -2 to Day 6.

Descriptive statistics summarized by exposure will be produced separately for all timepoints for all visits applicable for exhaled CO.

Actual values and percent changes from baseline in levels of exhaled CO will be listed and summarized. In addition line graphs will be produced for product means (and 95% CI) over all timepoints.

An ANCOVA model on exhaled CO will be used with terms for the baseline value, sex, average cigarette consumption over the previous 6 weeks prior to Admission and product.The LS means for each product along with the difference (CHTP - CC) and 95% confidence interval (CI) will be presented in the tables.

12.5.2.1.2 Urinary Biomarkers of Exposure

The Urinary Biomarkers of Exposure are total 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, total NNAL and NEQ. The urine parameters will be expressed as concentrations adjusted for creatinine. In addition, the quantity excreted over 24 hours for all Biomarkers of Exposure will be presented.

The values and percent changes for urinary BoExp in the quantity excreted over 24-hours and the concentration adjusted for creatinine will be listed and summarized. In addition line graphs will be produced for product means (and 95% CI) over all timepoints.

The analysis will compare the log-transformed urinary concentrations corrected for creatinine on Day 5 and the quantity excreted over 24-hours on Day 5 between the CHTP and CC arms. The descriptive statistics for each of the biomarkers of exposure of the secondary objectives, the statistical model and SAS code will be the same as described in Section **12.5.1.1** "**COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection**".

The hypothesis to be tested for each of the biomarkers of exposure of the secondary objectives will be the same as described in Section **12.5.1.2 "Confirmatory Analysis"**.

For the urinary concentrations, LS means for each product will be back-transformed by exponentiation and presented with the estimate and 95% CI of the reduction (calculated as the 100% - ratio).

In addition, a repeated measures ANCOVA model on the log-transformed NEQ will be used with terms for sex, average daily CC consumption over the last 6 weeks as reported during screening, product, timepoint, and the interaction between product and timepoint. The interaction term will be removed if $p > 0.1$.

The SAS code to be used is shown below:

```
Proc mixed data=_data_;
Class product sex cigarette_cons time_point;
Model log(NEQ) = sex cigarette_cons product product*time_point;
Repeated time_point / subject=subject type=un;
Lsmean product / diff alpha=0.05 cl;
Run;
```

LS means for each product will be back-transformed by exponentiation and presented with the estimate and 95% CI of the reduction (calculated as the 100% - ratio)..

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.1 | Analysis of Biomarkers of Exposure for the Primary and Secondary Objectives – FAS |
| 15.2.4.2 | Descriptive Statistics of Exhaled CO (ppm) – FAS |
| 15.2.4.3 | Descriptive Statistics of Urinary 1-OHP – FAS |
| 15.2.4.4 | Descriptive Statistics of Urinary Total NNN – FAS |
| 15.2.4.5 | Descriptive Statistics of Urinary 4-ABP – FAS |
| 15.2.4.6 | Descriptive Statistics of Urinary 1-NA – FAS |
| 15.2.4.7 | Descriptive Statistics of Urinary 2-NA – FAS |
| 15.2.4.8 | Descriptive Statistics of Urinary o-tol – FAS |
| 15.2.4.9 | Descriptive Statistics of Urinary CEMA – FAS |
| 15.2.4.10 | Descriptive Statistics of Urinary HEMA – FAS |

| TFL number | Title |
|---|---|
| 15.2.4.11 | Descriptive Statistics of Urinary B[a]P – FAS |
| 15.2.4.12 | Descriptive Statistics of Urinary HMPMA – FAS |
| 15.2.4.13 | Descriptive Statistics of Urinary Total NNAL – FAS |
| 15.2.4.14 | Descriptive Statistics of Urinary NEQ – FAS |
| 15.2.4.15 | Analysis of NEQ over the exposure period – FAS |
| | |
| FIGURES | |
| 15.1.2.1 | Urinary MHBMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.2 | Urinary 3-HPMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.3 | Urinary SPMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.4 | Exhaled CO Mean and 95% CI– FAS |
| 15.1.2.5 | 1-OHP Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.6 | Urinary 1-OHP Quantity excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.7 | Total NNN Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.8 | Urinary Total NNN Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.9 | 4-ABP Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.10 | Urinary 4-ABP Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.11 | 1-NA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.12 | Urinary 1-NA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.13 | 2-NA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.14 | Urinary 2-NA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.15 | o-tol Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.16 | Urinary o-tol Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.17 | CEMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.18 | Urinary CEMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |

| TFL number | Title |
|---|---|
| 15.1.2.19 | HEMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.20 | Urinary HEMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.21 | B[a]P Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.22 | Urinary B[a]P Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.23 | 3-HMPMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.24 | Urinary 3-HMPMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.25 | Total NNAL Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.26 | Urinary Total NNAL Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| 15.1.2.27 | NEQ Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.2.28 | Urinary NEQ Quantity Excreted Over 24 hours Geometric Mean and 95% CI– FAS |
| LISTINGS | |
| 15.3.3.1 | Listing of Biomarkers of Exposure and Sampling / Collection Times |

12.5.2.2 Nicotine and Cotinine Concentrations

The descriptive analysis will be the same as described in Section **12.5.1.1** "**COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection**".

The change from the Day -1 sample will be calculated for the Day 5 sample. The concentrations of nicotine and cotinine will be listed and summarized along with this change. Line graphs of the nicotine and cotinine concentration profiles across all study days showing mean and 95% CI will also be produced.

For nicotine and plasma concentrations the change from baseline (Day -1 sample at 08:00 PM - 09:30 PM)) on the Day 5 sample will be analyzed using an ANCOVA model with terms for baseline (Day -1) concentration, sex, average daily CC consumption over the last 6 weeks as reported during screening and product. The hypothesis to be tested for each of the biomarkers of exposure of the secondary objectives will be the same as described in Section **12.5.1.2 "Confirmatory Analysis"**.

Nicotine and cotinine will also be analyzed in a repeated measures ANCOVA model, as described in section "**12.5.2.1.2 Urinary Biomarkers of Exposure**".

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.16 | Descriptive Statistics of Plasma Cotinine and Nicotine Concentrations (ng/mL) – FAS |
| 15.2.4.17 | Analysis of Change from Day -1 Plasma Cotinine and Nicotine Concentrations on Day 5 – FAS |
| 15.2.4.18 | Analysis of Plasma Cotinine and Nicotine Concentrations over the exposure period – FAS |
| FIGURES | |
| 15.1.2.29 | Plasma Cotinine and Nicotine Concentrations (ng/mL) Mean and 95% CI – FAS |
| LISTINGS | |
| 15.3.3.3 | Listing of Plasma Cotinine and Nicotine Concentrations and Sampling Times |

12.5.2.3 CYP1A2 Activity

CYP1A2 activity will be measured in plasma on Day -1 and Day 5. In this study the CYP1A2 activity will be calculated using the molar ratio of PX and CAF, as described in Section **7.1.3** "**CYP1A2**". Descriptive statistics of the values and percent change on Day 5 from Day -1 and supportive listings will be provided.

The analysis will compare the Day 5 values between the CHTP and CC arms. An ANCOVA model will be used with terms for sex, average daily CC consumption over the last 6 weeks as reported during screening and product. The SAS code will be the same as described in Section **12.5.1.1** "**COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection**".

LS means for each product along with the difference (CHTP - CC) and 95% CI will be presented in the tables.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.26 | Descriptive Statistics of CYP1A2 Activity (%) – FAS |
| 15.2.4.27 | Analysis of CYP1A2 Activity (%) on Day 5 – FAS |
| LISTINGS | |
| 15.3.4.1 | Listing of CYP1A2 Activity and Changes from Baseline |

### 12.5.3 Exploratory Analysis

12.5.3.1 Questionnaires

12.5.3.1.1 Urge-to-Smoke Questionnaire of Smoking Urges Brief

The QSU-brief will be administered daily from Days -2 to 5.

All summaries, profiles and analysis will be presented for the CHTP and CC arms.

The change from baseline will be calculated for the total score and the two domain scores (relief and reward). The total score and two domain scores, along with the change from baseline will be summarized. The answers to the individual questions, along with the domain scores, total scores and changes from baseline will be listed.

The profiles of the raw means from baseline to Day 5 for the total score and two domain scores will be produced.

The analysis will compare each post baseline timepoint in the domain and total scores. A repeated measures ANCOVA model will be used with terms for baseline QSU-BRIEF score, sex, average daily CC consumption over the last 6 weeks as reported during screening, product, timepoint, and the interaction between product and timepoint. The interaction term will be removed if $p > 0.1$.

The SAS code to be used is shown below:

```
Proc mixed data=_data_;
Class product sex cigarette_cons time_point;
Model reduction = base_QSU sex cigarette_cons product
product*time_point;
Repeated time_point / subject=subject type=un;
Lsmean product / diff alpha=0.05 cl;
Run;
```

LS means for each product along with the difference (CHTP - CC) with 95% CI will be presented in the tables.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.20 | Descriptive Statistics of QSU-brief Factors and Total Scores – FAS |
| 15.2.4.21 | Analysis of QSU-brief Factors and Total Scores – FAS |
| FIGURES | |
| 15.1.2.31 | QSU-brief Factors and Total Scores Arithmetic Mean and 95% CI – FAS |
| 15.1.2.32 | QSU-brief Factors and Total Scores Arithmetic Least Squares Mean Differences and 95% CI – FAS |
| LISTINGS | |
| 15.3.6.11 | Listing of QSU-brief Questionnaire Results and Changes from Baseline |

12.5.3.1.2 Modified Cigarette Evaluation Questionnaire

The MCEQ will be administered daily from Days -2 to 5. The baseline will be the last assessment prior to 06:30 AM on Day 1.

All summaries, profiles and analysis will be presented for the CHTP and CC arm.

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

The profiles of the raw means from baseline to Day 5 for the five subcale scores will be produced.

The analysis will compare each post baseline timpoint in the subscales. A repeated measures ANCOVA model will be used with terms for baseline MCEQ score, sex, average daily CC consumption over the last 6 weeks as reported during screening, product, time-point, and the interaction between product and time-point.

The SAS code will be the same as described in Section **12.5.3.1.1** "**Urge-to-Smoke Questionnaire of Smoking Urges Brief**".

LS means for each product along with the difference (CHTP - CC) with 95% CI will be presented in the tables.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.24 | Descriptive Statistics of MCEQ Subscales – FAS |
| 15.2.4.25 | Analysis of MCEQ Subscales – FAS |
| FIGURES | |
| 15.1.2.35 | MCEQ Subscales Arithmetic Mean and 95% CI– FAS |
| 15.1.2.36 | MCEQ Subscales Arithmetic Least Squares Mean Differences and 95% CI – FAS |
| LISTINGS | |
| 15.3.6.13 | Listing of MCEQ Questionnaire Results and Changes from Baseline |

12.5.3.1.3 Minnesota Nicotine Withdrawal Questionnaire

The MNWS will be administered daily from Days -1 to 6 for the assessment of Day -2 to Day 5 as it is a 24-hour recall questionnaire. The baseline will be the last assessment prior to 06:30 AM on Day 1.

All summaries, profiles and analysis will be presented for the CHTP and CC arms.

The change from baseline will be calculated for both scores. The two scores, along with the change from baseline will be summarized. The answers to the individual questions, along with the two scores and changes from baseline will be listed.

The profiles of the raw means from baseline to Day 6 for the total scores will be produced.

The analysis will compare each post baseline timepoint for the two scores. A repeated meansures ANCOVA model will be used with terms for baseline score, sex, average daily CC consumption over the last 6 weeks as reported during screening, product, time-point, and the interaction between product and time-point.

The SAS code will be the same as described in Section **12.5.3.1.1** "**Urge-to-Smoke Questionnaire of Smoking Urges Brief**".

LS means for each product along with the difference (CHTP - CC) with 95% CI will be presented in the tables.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.22 | Descriptive Statistics of MNWS Total Scores – FAS |
| 15.2.4.23 | Analysis of MNWS Total Scores – FAS |

| TFL number | Title |
|---|---|
| FIGURES | |
| 15.1.2.33 | MNWS Total Scores Arithmetic Mean and 95% CI – FAS |
| 15.1.2.34 | MNWS Total Scores Arithmetic Least Squares Means and 95% CI – FAS |
| LISTINGS | |
| 15.3.6.12 | Listing of MNWS Questionnaire Results and Changes from Baseline |

12.5.3.2 Human Puffing Topography Parameters

The HPT assessments will take place on Day -2, Day 1 and Day 4 in the CHTP and CC arms, if CC are compatible with the HPT SODIM® device.

The per puff parameters are shown in Table 8 and the per cigarette parameters are shown in Table 9.

The per-cigarette parameters derived from the HPT assessments will be summarized along with their changes from baseline. The per-puff and per-cigarette parameters will be listed. In addition the geometric mean and 95% CI of the geometric mean of the per-cigarette parameters will be presented graphically.

The per-cigarette parameters will be analyzed on Days 1 and 4 separately using an ANCOVA model on the log-transformed HPT parameter with terms for log-transformed baseline score, sex, average daily CC consumption over the last 6 weeks as reported during screening, product.

The SAS code will be the same as described in Section **12.5.1.1** "**COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection**".

LS means for each product along with the reduction (i.e. 100% - ratio of CHTP : CC) and 95% CI will be presented in the tables.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.30 | Descriptive Statistics of HPT Parameters per Cigarette – FAS |
| 15.2.4.31 | Analysis of HPT per Cigarette – FAS |
| FIGURES | |
| 15.1.2.37 | HPT per Cigarette Parameters Geometric Mean and 95% CI – FAS |
| LISTINGS | |
| 15.3.7.1 | Listing of HPT Assessments |

12.5.3.3 Human Puffing Topography Questionnaire

The HPT questionnaire will be administered on Days -2, Day 1 and Day 4.

The individual responses will be listed.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| LISTINGS | |
| 15.3.7.2 | Listing of HPT Questionnaire Results |

12.5.3.4 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Days -1 and 6. In this study the CYP2A6 activity will be calculated using the metabolic ratio of trans 3' hydroxycotinine and cotinine, as described in Section **7.1.4** "**CYP2A6**". Descriptive statistics of the values and change on Day 6 from Day -1 and supportive listings will be provided.

The analysis will compare the Day 6 values (both absolute and change from baseline) between the CHTP and CC arms. An ANCOVA model will be used with terms for baseline, sex, average daily CC consumption over the last 6 weeks as reported during screening and product. .

The SAS code will be the same as described in Section **12.5.1.1** "**COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA in 24 hour collection**"

LS means for each product along with the difference (CHTP - CC) and 95% CI will be presented in the tables

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.28 | Descriptive Statistics of CYP2A6 Activity (%) – FAS |
| 15.2.4.29 | Analysis of CYP2A6 Activity – FAS |
| LISTINGS | |
| 15.3.6.15 | Listing of CYP2A6 Activity and Changes from Baseline |

12.5.3.5 Relationship between BoExp and NEQ

The analysis of the relationship between NEQ and the biomarkers for the primary and secondary objectives will be reported in a separate report as stated in Section 9 "**Changes from the Protocol Specified Statistical Analysis**".

12.5.3.6 Ames Mutagenicity Test

The 24 hour urine collection for the Ames mutagenicity test will be on Day -1 and Day 5.

Descriptive statistics of the values and change on Day 5 from Day -1 of the YG1024+S9 mutagenicity will be provided, along with listings.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.4.19 | Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (units) – FAS |
| LISTINGS | |
| 15.3.5.1 | Listing of Mutagenicity Results and Changes from Baseline |

### 12.5.4 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).

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

12.5.4.1 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.

All AEs occurring from the time of signing of informed consent will be recorded electronically. AEs will be tabulated and listed. However, during the screening period (prior to first product use), only study related AEs will be summarized. The AE listings will include all AEs captured in the database at any time during the study (including those from subjects who were not in the Safety Population).

AEs reported from subjects that have a first product use, but were not randomized will be summarized in a separate column with "Exposed but not using randomized product" as a column header.

Partial dates will not be imputed, but assumptions will be made as follows to assign to product-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 Screening. | Product-emergent |
| Partial date, e.g. --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening. | Not product-emergent |

12.5.4.2 Adverse Events

12.5.4.2.1 All Adverse Events

All AE tables will be presented by product.

A general summary table of AEs will be presented including:

- The number of events and the number and percentage of subjects reporting at least one AE.
- The number of events and the number and percentage of subjects reporting at least one study product –related AE, broken down by product relatedness (related to CHTP / CC) and expectedness.
- The number of events and the number and percentage of subjects reporting at least one AE broken down by severity including each subject only once with his worst severity.
- The number of events and the number and percentage of subjects reporting at least one SAE.
- The number of events and the number and percentage of subjects reporting at least one AE leading to any action taken, broken down by action taken related to the product (product use interrupted, product use reduced, product use withdrawn, none), treatment given (yes, no), study discontinuation, other action taken.

Additional summary tables of AEs will be presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by system organ class (SOC) and preferred term (PT) coded according to the Medical Dictionary for Regulatory Activities (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 with at least one AE related to product exposure and expectedness.
- The number of events and the number and percentage of subjects with at least one AE leading to product discontinuation or reduction.
- 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 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, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| 15.2.6.2 | 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 Study Product Exposure for Investigational Product (CHTP or CC) and Expectedness – Safety Population |
| 15.2.6.4 | Summary of Adverse Events Leading to Investigational Product (CHTP or CC) Discontinuation or Reduction by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.5 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.6 | Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.7 | Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.8 | Summary of Serious Adverse Events – Safety Population |
| LISTINGS | |

| TFL number | Title |
|---|---|
| 15.3.6.1.1 | Listing of Adverse Events |

Tables 15.2.6.4 - 15.2.6.6 and 15.2.6.8 will only be created if they contain 5 or more events.

12.5.4.2.2 Serious Adverse Events (Including Deaths)

A general summary table of SAEs will be presented using the same approach of AEs (see Section **12.5.4.2** "**Adverse Events**"), and including the number of events and the number and percentage of subjects reporting at least one SAE broken down by seriousness criteria (fatal, life-threatening, requires hospitalization, results in disability/incapacity, congenital anomaly/birth defect, other medically important event).

SAEs will also be listed in a separate listing by product.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.8 | Summary of Serious Adverse Events – Safety Population |
| 15.2.6.9 | Summary of Serious Adverse Events by System Organ Class and Preferred Term and Severity – Safety Population |
| LISTINGS | |
| 15.3.6.1.2 | Listing of Serious Adverse Events |

Tables 15.2.6.8 and 15.2.6.9 will only be created if they contain 5 or more events.

12.5.4.2.3 Adverse Events Leading to Discontinuation

Summaries will be presented for AEs leading to withdrawal, by product as described in Section **12.5.4.2** "**Adverse Events**",

AEs leading to withdrawal will also be listed in a separate listing by product.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.5 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| LISTINGS | |

| TFL number | Title |
|---|---|
| 15.3.6.1.3 | Listing of Adverse Events Leading to Study Discontinuation |

12.5.4.2.4 Laboratory Abnormalities

Laboratory abnormality data will be listed ordered by product, subject, parameter and time point. Details related to the toxicity grading of laboratory abnormalities are available in Section 12.5.4.4.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| 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 |

12.5.4.3 CHTP Product Quality Complaints

All events relating to the device type will be listed for each subject.

A summary table of product quality complaints will be presented by product, including:

- Number of product quality complaints and the number and percentage of subjects reporting at least one product quality complaint.
- Number of product quality complaints and the number and percentage of subjects categorized by product quality complaint (Defect CHTP 1.0 before use: [redacted].

Product quality complaints will be listed by product. Data collected during Screening will be listed but not summarized.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.10 | Summary of CHTP Product Quality Complaints – Safety Population |
| LISTINGS | |
| 15.3.6.2 | Listing of CHTP Product Quality Complaints |

12.5.4.4 Clinical Laboratory Evaluation

Table 20 below lists the hematology, clinical chemistry and urine analysis parameters to be assessed in this study.

**Table 20: List of Laboratory Safety Parameters**

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

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 from screening to after product-use it will be recorded as an AE.

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

Laboratory data will be summarized and listed by product, subject, parameter and time point at Screening, Day -1 and at Day of Discharge (Day 6 or day of withdrawal), together with numerical 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, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.13 | Summary of Clinical Chemistry Parameters – Safety Population |
| 15.2.6.14 | Summary of Hematology Parameters – Safety Population |
| 15.2.6.15 | 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 |

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

12.5.4.5.1 Prior and Concomitant Medication

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

All medications will be listed by product 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:

| 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 product. Concomitant medications will be summarized for the Safety Population showing the number (%) of subjects who used the medication at least once by product and by ATC 1st and 2nd levels and preferred drug name. Listings will display original dates (no imputation).

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.11.1 | Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population |
| 15.2.6.11.2 | Summary of Prior Medication by Preferred Drug Name – Safety Population |
| 15.2.6.12.1 | Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population |
| 15.2.6.12.2 | Summary of Concomitant Medication by Preferred Drug Name – Safety Population |
| LISTINGS | |
| 15.3.6.3 | Listing of Prior and Concomitant Medication |

12.5.4.5.2 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -3) and at the day of Discharge (Day 6 or at the day of withdrawal for withdrawn subjects) will be listed by product. Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. The number of subjects (%) with normal, abnormal and abnormal clinically significant results will be tabulated by body systems at Screening, Admission and day of Discharge.

Body weight recorded at Admission and day of 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** "**Categorical Variables**"), at Admission and Day of Discharge will be presented.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.20 | Summary of Physical Examination of Body Systems – Safety Population |
| LISTINGS | |
| 15.3.6.10 | Listing of Physical Examination Findings, Shift and Changes from Baseline |

12.5.4.5.3 Vital Signs

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

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 product for each study day. Vital signs data will be summarized together with changes from baseline.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.16 | Summary of Supine Vital Signs – Safety Population |
| 15.2.6.19 | Summary of Weight and BMI Measurements – Safety Population |
| LISTINGS | |
| 15.3.6.7 | Listing of Vital Signs Data and Changes from Baseline |

12.5.4.5.4 Spirometry

Spirometry parameters assessed during the study include:

- Measured forced expiratory volume in 1 second ($FEV_1$)
- Measured forced vital capacity (FVC)
- FEV1/FVC

- Predicted FEV1
- Percent of predicted FEV1 (% pred)
- Predicted FVC
- Percent of predicted FVC (% pred)
- Measurement interpretation (categories: normal, abnormal, abnormal clinically significant)

The above data are collected at Screening, Day -1, and Day of Discharge (Day 6 or day of withdrawal). At Screening, data are collected one hour after having stopped smoking. On day -1 and Day 6, spirometry has to be done prior to smoking.

Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set (**Hu and Cassano, 2000**).

Spirometry data values and normality evaluation will be listed by product and study day. Assessments performed after baseline will be listed together with change from baseline and shift in normality. Spirometry data from subjects who had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for $FEV_1$(L), $FEV_1$ (% pred), FVC(L), FVC(% pred), and $FEV_1$/FVC at baseline, and Discharge by product, and overall. Spirometry data will be summarized together with changes from baseline (pre-bronchodilator), and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.18 | Summary of Spirometry Results – Safety Population |
| LISTINGS | |
| 15.3.6.8 | Listing of Spirometry Data and Changes from Baseline |

12.5.4.5.5 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 using Fridericia's formula (QTcF) intervals; QRS duration; and heart rate; and normality evaluation (normal, abnormal, clinically relevant, together with any PMI comments to the abnormality).

The baseline for the ECG data will be the Screening value.

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

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.17 | Summary of ECG Measurements – Safety Population |
| LISTINGS | |
| 15.3.6.9 | Listing of ECG Data and Changes from Baseline |

12.5.4.5.6 Assessment of Cough

Cough questionnaire is assessed on a daily basis from Day -1 to Day 6. Questionnaire details are reported in Section **7.2.6** "**Cough Assessment**".

The number and % of subjects reporting cough will be summarized by product. 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 study arm, for all subjects who filled in the questionnaire. The answers to the open question(s) related to any other important observation will be listed.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

| TFL number | Title |
|---|---|
| TABLES | |
| 15.2.6.21 | Summary of Cough Assessments Over Study – Safety Population |
| 15.2.6.21.1 | Summary of Cough Assessments by Study Day – Safety Population |
| LISTINGS | |
| 15.3.6.14 | Listing of Cough Assessment Results |

# 13 ANALYSIS AND REPORTING

## 13.1 Interim Analysis and Data Monitoring

No interim analysis is planned on this study.

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

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

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

## 13.2 Safety Reporting

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

| TFL no. | Title |
|---|---|
| TABLES | |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.2.1 | Descriptive Statistics of Use of CHTP Product and CC – Safety Population |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| 15.2.6.2 | 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 Study Product Exposure and Expectedness – Safety Population |
| 15.2.6.4 | Summary of Adverse Events Leading to Study Product Discontinuation or Reduction by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.5 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.6 | Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.7 | Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.8 | Summary of Serious Adverse Events – Safety Population |
| 15.2.6.10 | Summary of CHTP product quality complaints – Safety Population |

## 13.3 Topline Results

Topline results, delivered with the draft TFLs, are 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 results are listed in the table below.

| TFL no. | Title |
|---|---|
| TABLES | |
| 15.2.3.1 | Analysis of Biomarkers of Exposure for the Primary Objectives – FAS |
| 15.2.3.2 | Analysis of Urinary Quantity Excreted of MHBMA, 3-HPMA and S-PMA over 24 hours on Day 5 – FAS |
| 15.2.3.3 | Descriptive Statistics of Blood COHb (%) – FAS |
| 15.2.3.3.1 | Descriptive Statistics of Blood COHb (%) by Sex – FAS |
| 15.2.3.3.2 | Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – FAS |
| 15.2.3.4 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) – FAS |
| 15.2.3.4.1 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS |
| 15.2.3.4.2 | Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS |
| 15.2.3.5 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) – FAS |
| 15.2.3.5.1 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS |
| 15.2.3.5.2 | Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS |
| 15.2.3.6 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) – FAS |
| 15.2.3.6.1 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS |
| 15.2.3.6.2 | Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS |
| 15.2.1.4.1 | Summary of Demographics and Other Baseline Characteristics – Safety Population |
| 15.2.1.4.2 | Summary of Demographics and Other Baseline Characteristics – FAS |
| 15.2.1.4.2.1 | Summary of Demographics and Other Baseline Characteristics by Sex – FAS |
| 15.2.1.4.2.2 | Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS |
| 15.2.6.1 | Summary of Adverse Events – Safety Population |
| 15.2.6.2 | Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population |

| TFL no. | Title |
|---|---|
| 15.2.6.3 | Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population |
| 15.2.6.4 | Summary of Adverse Events Leading to Study Product Discontinuation or Reduction by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.5 | Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.6 | Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population |
| 15.2.6.7 | Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population |
| 15.2.6.8 | Summary of Serious Adverse Events – Safety Population |
| FIGURES | |
| 15.1.1.1 | Blood COHb (%) Geometric Mean and 95% CI– FAS |
| 15.1.1.2 | MHBMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.1.3 | 3-HPMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |
| 15.1.1.4 | S-PMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– FAS |

## 13.4 Final Analyses

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

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

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

## 13.5 Clinical Trials.gov Reporting

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

| TFL no. | Title |
|---|---|
| TABLES | |
| 15.2.3.1 | Analysis of Biomarkers of Exposure for the Primary Objectives – FAS |
| 15.2.1.1 | Summary of Subject Disposition –All Screened Subjects |

## 14 DATA PRESENTATION

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

## 15 REFERENCES

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# 16 APPENDICES

## 16.1 Study Assessments

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

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -45 to Day -4** | **Day -3** | **Day -2** | **Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6 (Day of Discharge)** | **Day 6 to Day 13** |
| One informed consent for study participation/ICF for bio-banking | • | | | | | | | | | | |
| Two informed consent forms for long-term bio-banking | • | | | | | | | | | | |
| Admission/discharge | | • | | | | | | | | • | |
| Advice on the risk of smoking/smoking cessation advice/debrief | • | • | | | | | | | | • | |
| Inclusion/exclusion criteria | • | • | | | | | | | | | |
| Enrolment | | • | | | | | | | | | |

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -45 to Day -4** | **Day -3** | **Day -2** | **Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6 (Day of Discharge)** | **Day 6 to Day 13** |
| Randomization | | | | ● | | | | | | | |
| Demographics, medical history, concomitant diseases | ● | | | | | | | | | | |
| Vital signs a | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | |
| Physical examination b | ● | ● | | | | | | | | ● | |
| Spirometry c | ● | | | ● | | | | | | ● | |
| Prior/concomitant medication | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | |
| B/U: Hematology, clinical chemistry, urine analysis | ● | | | ● | | | | | | ● | |
| Electrocardiogram | ● | | | | | | | | | ● | |
| Chest X-ray d | ● | | | | | | | | | | |

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -45 to Day -4** | **Day -3** | **Day -2** | **Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6 (Day of Discharge)** | **Day 6 to Day 13** |
| B: HIV, hepatitis B and C | ● | | | | | | | | | | |
| U: Urine drug screening, urine cotinine screening test | ● | ● | | | | | | | | | |
| U: Pregnancy test | ● | ● | | | | | | | | ● | |
| Alcohol breath test | ● | ● | | | | | | | | | |
| FTND | ● | | | | | | | | | | |
| Identification of the current cigarette brand | ● | ● | | | | | | | | | |
| Questions about smoking history/habits and intention to quit smoking | ● | ● | | | | | | | | | |
| CHTP 1.0 demonstration | ● | | | | | | | | | | |
| CHTP 1.0 product test e | | ● | | | | | | | | | |
| CO breath test f | | | ● | ● | ● | ● | ● | ● | ● | | |

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -45 to Day -4** | **Day -3** | **Day -2** | **Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6 (Day of Discharge)** | **Day 6 to Day 13** |
| B: BoExp in blood: COHb g | | | ● | ● | ● | ● | ● | ● | ● | | |
| B: BoExp in plasma: nicotine, cotinine h | | | ● | ● | ● | ● | ● | ● | ● | | |
| B: CYP1A2 activity | | | | ● | | | | | ● | | |
| B: CYP2A6 activity c | | | | ● | | | | | | ● | |
| QSU-brief questionnaire i | | | ● | ● | ● | ● | ● | ● | ● | | |
| MNWS (revised version) k | | | | ● | ● | ● | ● | ● | ● | ● | |
| MCEQ (modified version; CHTP 1.0 and CC arms) k | | | ● | ● | ● | ● | ● | ● | ● | | |
| Assessment of cough | | | | ● | ● | ● | ● | ● | ● | ● | |
| AE/SAE recording | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Collection of CC butts for accountability | | ● | ● | ● | ● | ● | ● | ● | ● | | |
| Collection of used CHTP 1.0 sticks for accountability | | ● | | | ● | ● | ● | ● | ● | | |

| | Screening | Confinement Period | | | | | | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -45 to Day -4** | **Day -3** | **Day -2** | **Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6 (Day of Discharge)** | **Day 6 to Day 13** |
| Collection of used CHTP 1.0 sticks for plug and diffuser analysis | | | | | | | | ● | | | |
| HPT questionnaire (CHTP 1.0 and CC arms)l | | | ● | | ● | | | ● | | | |
| HPT | | | ● | | ● | | | ● | | | |
| B: Bio-banking m | | | | ● | | | | | | ● | |

Abbreviations: AE = Adverse event; B = Blood sample required; BoExp = Biomarker (s) of exposure; BMI = Body mass index; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; CYP2A6 = Cytochrome P450 2A6; FTND = Fagerström test for nicotine dependence; HIV = Human immunodeficiency virus; HPT: Human puffing topography; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event; U = Urine sample required

a. Systolic and diastolic blood pressure, pulse rate, and respiratory rate.
b. Physical examination and height (only at Screening), body weight and calculated BMI.
c. At Screening, spirometry needs to be done prior at least 1 hour after having stopped smoking. On Day -1 and Day 6, spirometry, and CYP2A6 blood sampling has to be done prior to smoking.

d. Pre-study chest X-ray (with anterior-posterior and left lateral views) may be used, if performed within 6 months prior to Screening.
e. On Day -3, CHTP 1.0 product test to be conducted after enrolment. After the product test, subjects not ready to use the CHTP 1.0 for 5 days will be discontinued.
f. CO breath test; Day -2 to Day 5: the test will be conducted once per day, preferably in the evening around 08:00 PM ± 1hour in conjunction with COHb tests, where applicable.
g. COHb; Assessments should be done in conjunction with CO breath tests, where applicable. Day -2 to Day 5: one blood sample in the evening around 08:00 PM ± 1 hour.
h. Nicotine/cotinine; Day -2 to Day 5 (both CHTP 1.0 and CC arms): one blood sample around 08:00 ± 1 hour.
i. QSU-brief: daily, from Day -2 to Day 5.
j. MNWS daily from Day -1 to Day 6.
k. MCEQ: daily from Day -2 to Day 5.
l. On Day -2, HPT and HPT questionnaire will be done in all subjects using CC compatible with the HPT SODIM® device. On Day 1 of the confinement period, HPT and HPT questionnaire will be done for every product use in all subjects in the CHTP 1.0 and CC arms. On Day 4 of the confinement period, HPT and HPT questionnaire will be done in all subjects using CC compatible with the HPT SODIM® device. Puffing topography with the HPT SODIM® device will not be done in subjects using CC that are incompatible with the HPT SODIM® device (e.g., slim CC).
m. Blood/plasma samples for further transcriptomics and lipidomics analyses will only be taken if additional consent for bio-banking is given by the subject.

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

| | Baseline Period | | Confinement Exposure Period | | | | |
|---|---|---|---|---|---|---|---|
| Study Day | Day -2 | Day -1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
| Collection Period | Day -2 to Day -1 | Day -1 to Day 1 | Day 1 to Day 2 | Day 2 to Day 3 | Day 3 to Day 4 | Day 4 to Day 5 | Day 5 to Day 6 |
| BoExp in urine | ● | ● | ● | ● | ● | ● | ● |
| Creatinine | ● | ● | ● | ● | ● | ● | ● |
| Ames mutagenicity test | | ● | | | | | ● |
| Bio-banking [a] | | ● | | | | | ● |

a Samples (5 tubes of 24-hour urine) will only be taken if additional consent for bio-banking is given by the subject.