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 1.2 (CHTP 1.2) compared to continuing to use combustible cigarettes, for 5 days in confinement followed by 85 days in an ambulatory setting.

Study Product: Carbon Heated Tobacco Product 1.2 (CHTP 1.2)

Sponsor Reference No.: P2R-REXA-07-EU

Sponsor:
Philip Morris Products S.A.
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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 Statistical Analysis Plan (SAP) has been developed to supplement the statistical analyses described in the clinical study protocol version 5.0 dated 05 December 2016.

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

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

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

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (**ICH Guideline E9, 1998**).
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" **(ICH Guideline E3, 1995**).
- Electronic case report forms (eCRF) Version 6.0 dated 12 July 2016.
- Biostatistical Addendum – Subject Randomization List version 4.0 (30 Sep 2015).

3.1 Revision History

Version	Date of Revision	Revision
1.0	27Jan2017	Final Version 1

4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used within this SAP and TLF shells.

11-DTX-B2	11-dehydro-thromboxane B2
1-NA	1-aminonaphthalene
2-NA	2-aminonaphthalene
3-HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
4-HNE	4-hydroxy-2-nonenal
8-epi-PGF2α	8-epi-prostaglandin F2α
8-OHdG	8-hydroxy-2'-deoxyguanosine
AE	Adverse event
AE/SAE	Adverse Event/ Serious Adverse Event
ANCOVA	Analysis of Covariance
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ATC	Anatomical Therapeutic and Chemical
BLOQ	Below the Lower limit of Quantification
BMI	Body Mass Index
BoExp	Biomarkers of exposure
CAF	Caffeine
CC	Combustible Cigarettes
CEMA	2-cyanoethylmercapturic acid
CHTP	Carbon Heated Tobacco Product
CI	Confidence Interval
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
CRF	Case report form
CRO	Contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CTMS	Clinical trial management system
CV	Coefficient of Variation
CVD	Cardiovascular diseases
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EOS	End of Study
FAS	Full Analysis Set

FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced Expiratory Volume in 1 second
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HEMA	2-hydroxyethyl mercapturic acid
HIV	Human Immunodeficiency Virus
HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
HPHCs	Harmful and potentially harmful constituents
hs-CRP	High sensitive C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational product
ISO	International Organization for Standardization
ITUQ	Intent to Use Questionnaire
IXRS	Interactive Web Response System
LDL	Low density lipoprotein
LLOQ	Lower Limit of Quantification
LS	Least Squares
mCEQ	modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenyl mercapturic acid
MPO	Myeloperoxidase
MR	Mean Ratio
n	Number of subjects
NEQ	Nicotine Equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1butanone
NNN	N-nitrosonornicotine
NRT	Nicotine replacement therapy
o-tol	o-toluidine
PGF2α	Prostaglandin F2α
PI	Principal Investigator
PMI	Philip Morris International
PP	Per protocol
PT	Preferred Term
PX	Paraxanthine
QC	Quality control
QSU-brief	Questionnaire of Smoking Urges
QTcB	QT Interval Corrected using Bazett's Formula

QTcF	QT Interval Corrected using Fridericia's Formula
RRP	Reduced risk products
SA	Smoking Abstinence
SAP	Statistical Analysis Plan
S-BMA	S-benzylmercapturic acid
SD	Standard deviation
SDTM	Standard Data Tabulation Modul
SES	Socio-Econonomic Status
sICAM-1	Soluble inter-cellular adhesion molecule-1
SOC	System Organ Class
SOP	Standard Operating Procedure
S-PMA	S-phenylmercapturic acid
T	Time point
TAC	Total anti-oxidant capacity
TC	Total cholesterol
TFL	Tables, Figures, and Listings
TG	Triglycerides
Total 1-OHP	Total 1-hydroxypyrene
Total 3-OH-B[a]P	Total 3-hydroxybenzo(a)pyrene
ULOQ	Upper Limit of Quantification
VAS	Visual Analogue Scale
WBC	White blood cell (count)
WHO	World Health Organisation
YG1024+S9	Ames Mutagenicity Test

The following special terms are used in this SAP:

Admission period	Day -3 until start of baseline period.
Baseline period	06:30 AM at Day -2 until 06:29 AM of Day 1.
Carbon Heated Tobacco Product 1.2 (CHTP 1.2)	CHTP 1.2 is a non-menthol tobacco stick which is comparable in shape and form, and is used in a similar manner to a combustible cigarette except that the tobacco contained in the CHTP 1.2 is heated by a Carbon Heat Tip and not burned like in a combustible cigarette.
Combustible cigarette (CC)	The term 'combustible cigarette' refers to commercially available cigarettes (manufactured) and excludes cigars, pipes, bidis, and other nicotine-containing products.
Completer	A suibject is considered to have completed Confinement, period 2, 3 and 4 if he/she did not discontinue before Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit respectively, and Completed safety follow-up.
Day of Discharge in the Confinement setting	Day 6 or early discontinuation in confinement.
Day of Discharge in the Ambulatory setting	Second day of Day 90 Visit.
Enrolment	On Day -3 for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily met.
Enrolled	A subject is considered as being enrolled once he/she is declared for being enrolled in the IxRS.
Exposure period	In the confinement setting: 06:30 AM of Day 1 until the time of discharge on Day 6. In the Ambulatory Setting: from Discharge on Day 6 until Discharge at Day 90 Visit.
Randomization	Allocation of the respective arm 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 arm they are randomized to prior to the first product use.
Safety follow-up	After the time of Discharge at Day 90 Visit or the date of early termination, a 28-day safety follow-up will be done for the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site.
Screening failure	Subjects who are not enrolled will be considered a screening failure and will be replaced by other subjects. Re-screening will not be permitted.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective and Endpoints

1. To demonstrate the reduction of biomarkers of exposure (BoExp) to selected harmful and potentially harmful constituents (HPHCs) in smokers switching from combustible cigarettes (CC) to CHTP 1.2 as compared to smokers continuing to use CC for 5 days.

   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 HPHCs in blood (expressed as % of saturation of hemoglobin):
     - BoExp to carbon monoxide (CO): carboxyhemoglobin (COHb)
2. To demonstrate the reduction of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC for 90 days.

   Endpoint (Day 90 Visit):

   - BoExp to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK):
     - total NNAL level (expressed as concentration adjusted for creatinine in 24-hour urine).

5.2 Secondary Objectives and Endpoints

1. To evaluate self-reported nicotine/tobacco product use throughout the entire exposure period, including dual-use in an ambulatory setting in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC.

   Endpoint (measured daily):

   - Number of CC or CHTP 1.2 used daily as reported on the usage log during the confinement period, and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use diary during the ambulatory period

2. To determine the reduction of various BoExp to HPHCs in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC for 5 days and for 90 days.

   Endpoints (Day 5 to Day 90 Visit):

   - BoExp to HPHCs in urine (expressed as quantity excreted or concentration adjusted for creatinine in 24-hour urine):
     - MHBMA (Day 90 Visit only)
     - 3-HPMA (Day 90 Visit only)
     - S-PMA (Day 90 Visit only)
     - Total NNAL (Day 5 only)

- BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene (Day 5, Day 90 Visit)
- BoExp to pyrene: total 1-hydroxypyrene (total 1-OHP) (Day 5, Day 90 Visit)
- BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN) (Day 5, Day 90 Visit)
- BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP) (Day 5, Day 90 Visit)
- BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA) (Day 5, Day 90 Visit)
- BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA) (Day 5, Day 90 Visit)
- BoExp to o-toluidine: o-toluidine (o-tol) (Day 5, Day 90 Visit)
- BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA) (Day 5, Day 90 Visit)
- BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA) (Day 5, Day 90 Visit)
- BoExp to crotonaldehyde: 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA) (Day 5, Day 90 Visit)

- BoExp to CO:
  - CO in exhaled breath (expressed as ppm) (Day 5, Day 90 Visit)
  - COHb in blood (expressed as % of saturation of hemoglobin) (Day 90 Visit only)

3. To describe the levels of BoExp over the entire exposure period in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC.

   Endpoints (Day 1 to Day 90 Visit):

   - BoExp to CO:
     - CO in exhaled breath (expressed as ppm)
     - COHb in blood (expressed as % of saturation of hemoglobin)
   - BoExp to HPHCs in urine (expressed as quantity excreted and concentration adjusted for creatinine in 24-hour urine):
     - MHBMA
     - 3-HPMA
     - S-PMA
     - Total NNAL
     - Total 1-OHP
     - Total NNN
     - 4-ABP
     - 1-NA
     - 2-NA
     - o-tol
     - CEMA
     - HEMA
     - 3-hydroxybenzo(a)pyrene

- HMPMA

4. To describe the levels of nicotine over the entire exposure period in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC.
   Endpoints (Day 1 to Day 90 Visit):
   - Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide), expressed as concentration adjusted for creatinine in 24-hour urine
   - Nicotine and cotinine plasma concentrations

5. To determine the changes over the entire exposure period in lung functions in smokers switching from CC to the CHTP 1.2 as compared to those continuing to use CC
   Endpoint (Day 6 and Day 90 Visit):
   - Spirometry (pre- and post-bronchodilator):
     - forced expiratory volume in 1 second (FEV_1),
     - forced vital capacity (FVC),
     - FEV_1/FVC,
     - forced expiratory flow (FEF 25-75)

   Endpoint (Day 1 to Day 90 Visit):
   - Cough assessment by Visual Analog Scale (VAS) and Likert Scales and one open question.

6. To monitor selected cardiovascular clinical risk endpoints over the entire exposure period in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC
   Endpoints (Day 6 to Day 90 Visit):
   - Systolic and diastolic blood pressure on Day 6, at Day 30 Visit, Day 60 Visit, and Day 90 Visit
   - High sensitive C-reactive protein (hs-CRP), blood glucose, myeloperoxidase (MPO), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) in serum at Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Fibrinogen, homocysteine in plasma at Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Hemoglobin A1c (HbA1c) in blood at Day 90 Visit.
   - Apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) in serum at Day 90 Visit.
   - Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6, at Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - White blood cell (WBC) and platelet counts in blood on Day 6, at Day 30 Visit, Day 60 Visit, and Day 90 Visit.

- 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5, at Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
- Body weight and waist circumference at Day 90 Visit.

7. To evaluate the changes in levels of selected clinical risk endpoints related to oxidative stress over the entire exposure period in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC

   Endpoints (Day 5 to Day 90 Visit):

   - Epi-prostaglandin F2α (8-epi-PGF2α) in 24-hour urine on Day 5, at Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
   - Ratio of 8-epi-prostaglandin F2α (8-epi-PGF2α) to prostaglandin F2α (PGF2α) in plasma on Day 5 and at Day 90 Visit.
   - 8-Hydroxy-2'-deoxyguanosine (8-OHdG) in 24-hour urine on Day 5, at Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
   - 4-Hydroxy-2-nonenal (4-HNE) in serum on Day 5 and at Day 90 Visit [a].
   - Total anti-oxidant capacity (TAC) in serum on Day 5 and at Day 90 Visit.

   [a] Samples for 4-HNE analysis have been collected but will not be analyzed due to the failure to develop a selective and quantitative assay

8. To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC

   Endpoint (Day 5 and Day 90 Visit):

   - Molar metabolic ratio of paraxanthine/caffeine in plasma

9. To monitor the safety profiles associated with CHTP 1.2 and CC during the study

   Endpoints:

   - Adverse events (AEs) / serious adverse events (SAEs) and incidence of CHTP 1.2 malfunctions and misuse, including the incidence of heat source drop off
   - Vital signs
   - 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 1.2 as compared to smokers continuing to use CC
   - Excretion of mutagenic material in 24-hour urine

   Endpoints:

- Ames mutagenicity test (YG1024+S9): Day 5 and Day 90 Visit.

- Subjective effects of smoking

  Endpoints:

  - Questionnaire of Smoking Urges (QSU), (brief version): Day 1 to Day 90 Visit.
  - Fagerström Test for Nicotine Dependence (FTND), (revised version): Day 90 Visit.
  - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ): Day 1 to Day 90 Visit.

- Cytochrome P450 2A6 (CYP2A6) enzymatic activity

  Endpoints:

  - the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine: Day 6 and Day 90 Visit.

- Intent to Use of CHTP 1.2

  Endpoints:

  - Intent to Use of CHTP 1.2 Questionnaire (ITUQ): only in smokers switching from CC to CHTP 1.2: Day 6 and Day 90 Visit

2. To describe the CHTP 1.2 use over the entire exposure period according to the product preference of the subject

   Endpoint (daily):

   - Number of CC or CHTP 1.2 used daily as reported on the usage log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use diary during the ambulatory period according to product preference

3. To assess the smokers' mental state for the intention to quit

   Endpoint (Day 90 Visit):

   - Prochaska "Stage of Change" Questionnaire

4. To monitor BoExp and clinical risk endpoints in subjects who attempt to quit using tobacco products according to the time since they quit [a]

   Endpoints:

   - BoExp: MHBMA, S-PMA, 3-HPMA, COHb, and total NNAL
   - CO (expressed as ppm) in exhaled breath
   - Selected clinical risk endpoints (hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, HbA1c, sICAM-1, WBC, platelet count, Apo A1, Apo B, 11-DTX-B2, and clinical risk endpoints related to oxidative stress) in respective body matrix

[a] The reporting of the objective will be the subject of an appendix to the main clinical study report.

5.4 Study Hypotheses And Evaluation Criteria

5.4.1 Hypotheses

The hypothesis to be tested is that the geometric means of each of the BoExp levels for the CHTP 1.2 is lower relative to CC. For BoExp measured as primary endpoints, this hypothesis will be tested after 5 days of exposure for MHBMA, 3-HPMA, S-PMA, and COHb, and after 90 days of exposure for total NNAL.

5.4.2 Evaluation Criteria

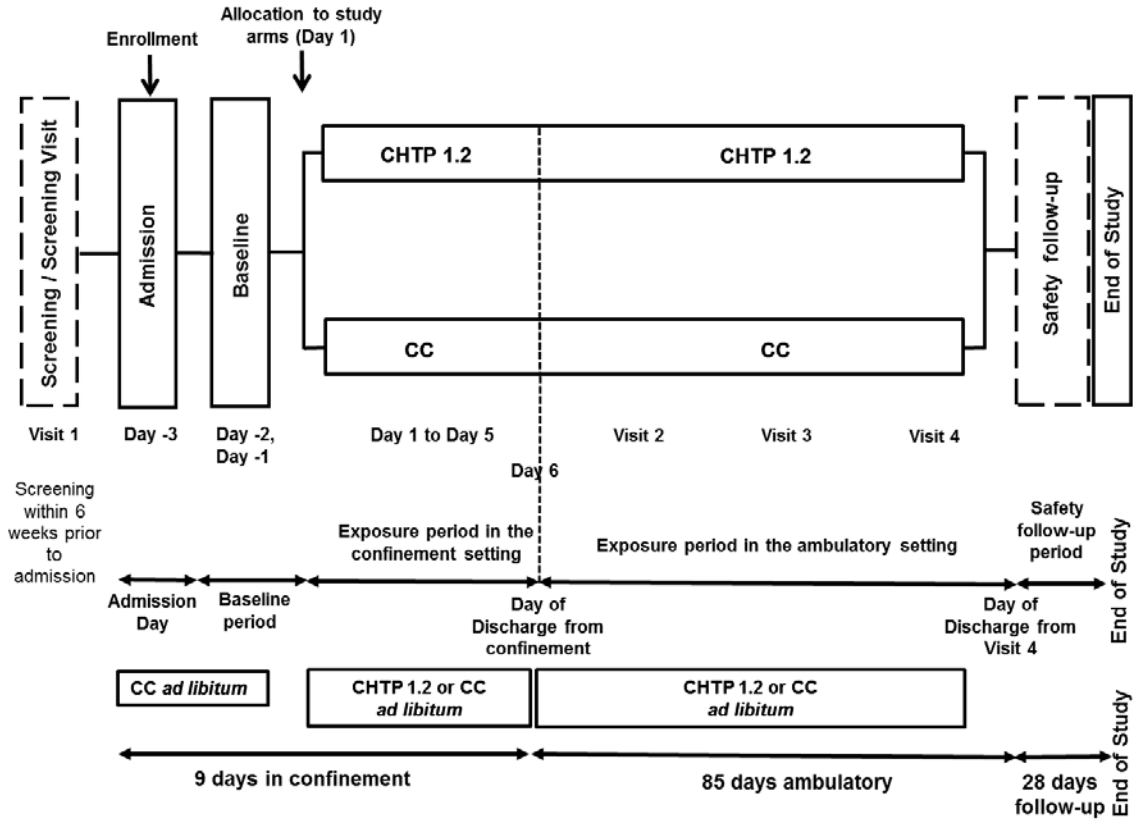
The study is designed to be able to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb after 5 days of exposure, and in total NNAL after 90 days of exposure in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability.

6 INVESTIGATIONAL PLAN

6.1 Study Design

A randomized, controlled, open-label, 2-arm, parallel group, study design with a stratified randomization by sex and average daily CC consumption over the last 6 weeks as self-reported at Admission (smoking 10 to 19 CC/day vs. > 19 CC/day) (**Figure 1**).

Figure 1 Study Flowchart



Abbreviations: CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CC= Combustible Cigarette(s)

- The Screening Period (from Day -45 until Admission on Day -3):

The Screening Period covers 6 weeks prior to Admission to the site. A demonstration of CHTP 1.2 (without product use) will be done by the site staff during the Screening Visit (Visit 1). At the Screening Visit, spirometry needs to be done at least 1 hour after having stopped smoking.

- 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, all eligible subjects will be enrolled and perform a product test using up to 5 CHTPs 1.2. However, before smoking and the product testing, the sample for CYP2A6 activity has to be taken. After the product test, subjects not willing and ready to use the CHTP 1.2 will be discontinued. After the sample for CYP2A6 activity has been taken, and the product test has been performed, smokers will be allowed to smoke their single preferred brand of CC *ad libitum* until 11.00 PM. Use of any tobacco/nicotine containing product other than CC and CHTP 1.2 for the product test will not be allowed after Admission.

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

All subjects will continue smoking their CC *ad libitum*. Twenty four-hour urine collection for Day -2 will start in the morning of Day -2 ending in the morning of Day -1. Twenty four-hour urine collection for Day -1 will start in the morning of Day -1 ending in the morning of the Day 1. On Day -2 and Day -1, smoking will be allowed from 06:30 AM until around 11:00 PM. However, on Day -2, smoking will be allowed only after the Cough Questionnaire has been completed.

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

- CHTP 1.2 arm: ~80 subjects, *ad libitum* use of CHTP 1.2
- CC arm: ~40 subjects, *ad libitum* use of their own preferred CC brand

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

- The Exposure Period (from Day 1, 06:30 AM until Discharge at Day 90 Visit):

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

- The Exposure Period in the Confinement Setting (from Day 1, 06:30 AM until the time of Discharge on Day 6):

  The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product from 06:30 AM until around 11:00 PM each day in the CHTP 1.2 and CC arms.

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

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

  Procedures on Day 6 will be conducted before discharge of the subject from the clinic after 9 days in a confined setting. Use of products will be allowed on Day 6 according to product allocation, but only after the sample for CYP2A6 activity has been taken, the cough assessment has been completed, and spirometry has been performed.

  Subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days.
- The Exposure Period in the Ambulatory Setting (from Discharge on Day 6 until Discharge at Day 90 Visit):

  Subjects will be required to make three visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each visit will cover 2 consecutive days on site.

For Day 30 Visit and Day 60 Visit, the subject will check-in in the morning on the first day of the respective visit and will check-out on the second day of the visit. For Day 90 Visit, the subject will check-in in the morning on the first day of the visit, and will be discharged on the second day of the visit after having performed all the safety examination procedures.

Twenty four-hour urine will be collected at each visit (Day 30 Visit, Day 60 Visit, and Day 90 Visit) at the site. The collection of 24-hour urine will start on the first day of the respective visits and will end 24 hours later on the following day. On the first day of Day 30 Visit, Day 60 Visit, and Day 90 Visit, subjects in the CHTP 1.2 and CC arms will be allowed to use their assigned product from the time of check-in until 11:00 PM. On the second day of Day 30 Visit and Day 60 Visit, product use will be allowed from 06:30 AM. The exposure period to the assigned IP will end at 11:00 PM on the first day of Day 90 Visit.

On the second day of Day 90 Visit, subjects who wish to smoke CC or use other nicotine/tobacco-containing products will be allowed to do so, but only after the end of 24-hour urine collection and after spirometry and sampling for CYP2A6 activity have been performed.

During the visits, the dispense and use of CHTP 1.2 will be strictly forbidden for subjects in the CC arm.

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

During the confinement and ambulatory settings:

- Any subject, who wants to attempt to quit using any tobacco products during the study (e.g., CHTP 1.2 and CC) will be encouraged to do so and will be referred to appropriate medical services. This will not affect subject's financial compensation, and the subject will remain in the study.
- The Safety Follow-up Period (from Discharge at Day 90 Visit until the End of the Safety Follow-up Period):

  After Discharge at Day 90 Visit or the date of early termination, subject will enter a 28-day Safety Follow-up Period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the study. 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.

AEs with onset after the end of the Safety Follow-Up Period and considered related to the IP might be reported to the Sponsor. Such AEs may not be part of the study report.

SAEs spontaneously reported to the PI after the end of the Safety Follow-Up Period and considered related to the IP must also be reported to the Sponsor. Such SAEs may not be part of the study.

The individual end of study (EOS) date for a subject is defined as either the Discharge at Day 90 Visit or the date of early termination followed by the 28-day Safety Follow-up Period.

The EOS of the entire study is the last individual EOS time point during the study.

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 ≥ 28 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 the Screening Visit and Admission, respectively, based on self-reporting. The smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).
6. The subject has been smoking at least for the last 10 years.
7. The subject does not plan to quit smoking in the next 6 months as assessed by Prochaska “Stage of Change” Questionnaire.
8. The subject is ready to comply with the study protocol (e.g., to use CHTP 1.2).

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 significant 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 test results assessed as Grade 2 and deemed clinically significant by investigators or Grade 3 and higher (as per the Common Terminology Criteria for Adverse Events [CTCAE]).
5. The subject has (FEV1/FVC) < 0.7 and FEV1 < 80% of the predicted value at post-bronchodilator spirometry.
6. The subject has (FEV1/FVC) < 0.75 (post-bronchodilator) and reversibility in FEV1 (that is both > 12% and > 200 mL from pre- to post-bronchodilator values).
7. The subject has a body mass index (BMI) < 18.5 or ≥ 32 kg/m2.
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,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.
12. The subject has a positive urine drug test.
13. The subject has positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B or hepatitis C.
14. The subject has donated or received whole blood or blood products within 3 months prior to Admission.
15. The subject is a current or former employee of the tobacco industry or their first-degree relatives (parent, sibling, child).
16. 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).
17. The subject has participated in a clinical study within 3 months prior to the Screening Visit.
18. The subject has been previously screened in this study.
19. For women only: Subject is pregnant (does have positive pregnancy tests at the Screening or at Admission) or is breast feeding.

20. 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, hormonal contraception, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-up Period. Hysterectomy, tubal ligation, bilateral oophorectomy or post-menopausal status are reasons for not needing to use birth control. 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

At the end of the Baseline period enrolled subjects will be randomized using an interactive web and voice response system (IxRS) on Day -1 at any time during the day. Subjects will be informed of their randomized study arm in the morning of Day 1, prior to 06:30 AM (the start of the exposure period). Subjects will be randomized to one of the 2 study arms: CHTP 1.2 or CC in a 2:1 ratio.

Stratified randomization will be conducted by sex and by average daily CC consumption over the last 6 weeks prior to Admission as self-reported (smoking 10 to 19 CC/day vs. > 19 CC/day). In each arm, each sex and each of the smoking strata will 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 the database lock [a] whichever comes last.
PMI Data Manager	After the finalization of PMI blind database review [a].
PMI Clinical Scientist	After the finalization of PMI blind database review [a].

[a] Data will be accessible blinded to randomization arm and to product use by means of a dummy randomization or masking.

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

During the confinement period, adherence to product allocation for both study arms will be ensured by strict distribution of the products (stick by stick) and collection of the CC butts and CHTP 1.2 after each use. Distribution and return of these products will be documented in appropriate logs.

During the ambulatory period, from Discharge on Day 6 until Discharge at Day 90 Visit, subjects in both study arms will capture the number of the product used (e.g., menthol and non-menthol CC, CHTP 1.2, or any other tobacco /nicotine-containing products including nicotine replacement therapy [NRT]) in the product use diary on a daily basis. The product use diary will be supplied by Sponsor and distributed to the subjects by the study site collaborators. The data captured in the product use diary will serve as the method to assess adherence in both arms. On Day 6, the adherence to the assigned product will be ensured using both the accountability log (from 06:30 AM until Discharge) and the product use diary (in the subjects daily report of product use). In case of discrepancy between the log and the diary entries, the diary will be considered as the primary source data.

6.3.3.1 Dual Use

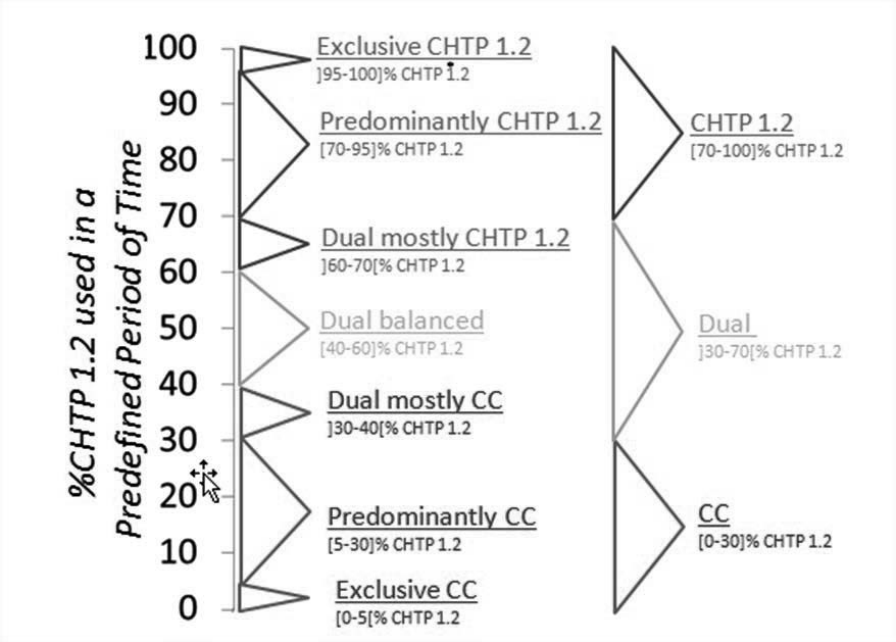
Although subjects are being requested to use solely the product allocated to them in their respective study arm, it is considered that during the ambulatory period not all subjects randomized to CHTP 1.2 arm might be exclusively using CHTP 1.2 at all times during the study. Subjects may concomitantly use CHTP 1.2 and CC (dual-use).

To assess dual-use of CHTP 1.2 and CC, PMI has defined product use categories defined by the percentage of the reported CHTP 1.2 Tobacco Sticks consumption during each time period of interest. The percentage use of CHTP 1.2 will be calculated by:

$$100\ x\ \frac{Total\ number\ of\ CHTP\ 1.2\ products\ used}{Total\ number\ of\ CHTP\ 1.2\ products\ used + Total\ number\ of\ CC\ smoked}$$

Product use categories are summarized in **Table 7,** and **Figure 2** presents a detailed overview of the definition of the product use categories.

Figure 2 Product Use Pattern Categorization



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

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.

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

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

7.1 Biomarkers

7.1.1 Biomarkers of Exposure

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

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

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 [mg] = (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:

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

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 ratio will be reported as a percentage.

If either of the PX or CAF concentration is below the lower limit of quantification (BLOQ) 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 ratio will be reported as a percentage.

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

7.2 Product Use Diary

A product use diary will be used for the documentation of the used CHTPs 1.2, CCs (menthol and non-menthol), used NRTs product, or the use of other nicotine/tobacco containing products. All subjects in both arms must complete this diary on a daily basis on and from Day 6 until the time of Discharge at Day 90 Visit. Subjects will be trained by site staff in the use of this diary during the confinement period at the time the diary is delivered to the subject.

7.3 Spirometry

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

7.4 Questionnaires

All used questionnaires, except cough VAS and SES, are available as a validated questionnaire in Polish.

7.4.1 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 and at Day 90 Visit to determine subject's potential dependence on nicotine with regards to CC at the Screening Visit and the assigned product at Day 90 Visit.

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 ▪ 6 to 30 minutes ▪ 31 to 60 minutes ▪ After 60 minutes	3 2 1 0
2	Do you find it difficult to refrain from smoking in places where it is forbidden?	▪ Yes ▪ No	1 0
3	Which cigarette would you hate most to give up?	▪ The first one in the morning ▪ Any other	1 0
4	How many cigarettes per day do you typically smoke?	▪ 10 or less (up to ½ pack) ▪ 11 to 20 (a little more than ½ pack, up to a full pack) ▪ 21 to 30 (a little more than a pack, up to 1½ packs) ▪ 31 or more (more than 1½ packs)	0 1 2 3
5	Do you smoke more frequently during the first hours after waking than during the rest of the day?	▪ Yes ▪ No	1 0
6	Do you smoke if you are so ill that you are in bed most of the day?	▪ Yes ▪ No	1 0

7.4.2 Socio-Economic Status

On Day 4 of the confinement period, subjects will be asked a series of questions related to their education, occupational status, size and annual income of their household (**King et al, 2011**).

7.4.3 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, and at the first day of Day 30 Visit, Day 60 Visit and Day 90 Visit 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.

7.4.4 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, and at the first day of Day 30 Visit, Day 60 Visit and Day 90 Visit 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 awake?	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.

7.4.5 The Intent to Use Questionnaire (ITUQ)

The Intent to Use Questionnaire (**Philip Morrris Products S.A, 2015**) is a self-report questionnaire that assesses subjects' intention to use CHTP 1.2 in smokers switching from CC to CHTP 1.2. The ITUQ comprises 3 sets of items:

- 1 item assessing the likelihood of using CHTP 1.2 regularly
- 5 items assessing the likelihood of using CHTP 1.2 with or without other tobacco-nicotine products including CC. Only subjects who provide response to the item assessing the likelihood of using CHTP 1.2 regularly with "Very unlikely" to "Definitely" will be asked to answer these items

Each item in these 2 sets will be rated on a 6-point scale ranging from "definitely not" to "definitely" with higher scores indicating greater likelihood to use CHTP 1.2 in the respective aspect.

- 1 item assessing how soon the subject will begin to use CHTP 1.2. Only subjects who provide response to the item assessing the likelihood of using CHTP 1.2 regularly with "Very unlikely" to "Definitely" will be asked to answer this item

This item will be rated on an ordinal scale with 6 timeframe categories ranging from "Within one week" to "Never". No composite index of intent to use will be constructed from this questionnaire. The assessments will be performed on Day -2, Day 6 and Day 91.

7.4.6 Prochaska "State of Change" Questionnaire: Intention to Quit Smoking

The Prochaska's "Stage of Change" Questionnaire will be used to assess the smokers' mental state for the intention to quit (**DiClemente et al, 1991; Velicer et al, 1995**).There are 5 stages of change describing smokers and former smokers: 1. Precontemplation, 2. Contemplation. 3. Preparation. 4. Action. 5. Maintenance.

- In the "Precontemplation" stage, the individual does not recognize smoking as a problem
- In the "Contemplation" stage, the individual is gathering information about smoking, such as contacting a health care provider or a tobacco quit line for information on the effects of smoking or smoking cessation consequences. During this stage, the stress and inconvenience of quitting smoking is greater than the immediate and possible long-term health effects of continuing smoking
- In the "Preparation" stage, intention and behavior begin to come together and the subject is preparing to enter into action in the next 30 days. It is necessary for the subject to recognize the benefits of not smoking, before a subject can enter the "Action" stage and as a result, changes his/her smoking behavior
- After six months of not smoking, the individual reaches the "Maintenance" stage when different skills may be needed to prevent relapse from smoking
- The structure of the questionaire is shown in Figure 3 and the scoring algorithm is shown in Table 5.

Figure 3: Structure of Prochaska's "Stage of Change" Questionnaire

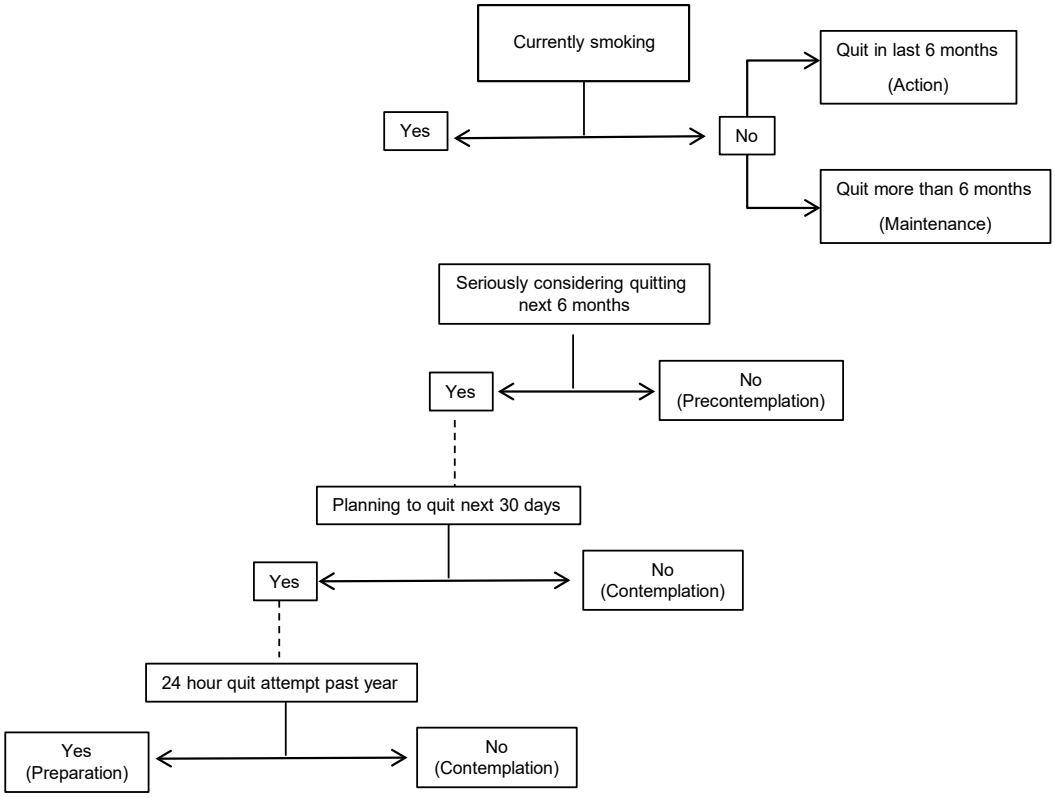


Table 5: Scoring algorithm

Assessment:

1. Are you currently a smoker?
   A) Yes, I currently smoke
   B) No, I quit within the last 6 months
   C) No, I quit more than 6 months ago
   D) No, I have never smoked

Smokers only:
2. In the last year, how many times have you quit smoking for at least 24 hours? ___
3. Are you seriously thinking of quitting smoking?
   A) Yes, within the next 30 days
   B) Yes, within the next 6 months
   C) No, not thinking of quitting

Scoring Sheet (do not read to subject):

1. Are you currently a smoker?
   A) Yes, I currently smoke
   B) No, I quit within the last 6 months (ACTION STAGE)
   C) No, I quit more than 6 months ago (MAINTENANCE STAGE)
   D) No, I have never smoked (NONSMOKER)

Smokers only:
2. In the last year, how many times have you quit smoking for at least 24 hours? -------
3. Are you seriously thinking of quitting smoking?
   A) Yes, within the next 30 days (PREPARATION STAGE if they have one 24-hour quit attempt in the past year, if there was no quit attempt in the past year, then CONTEMPLATION STAGE)
   B) Yes, within the next 6 months (CONTEMPLATION)
   C) No, not thinking of quitting (PRECONTEMPLATION)

-

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

7.4.7 Cough Assessment

Subjects will be asked to self-report and to assess the respiratory symptom "cough" on a VAS, on three Likert scales, and with an open question. Assessment of cough reflecting the cough symptoms in the last 24 hours will be conducted irrespective of the time of product use.

Subjects will be asked if they have experienced a regular need to cough, e.g., whether they have coughed several times in the previous 24 hours prior to assessment. If the answer is "yes", subjects will be asked to complete a VAS, 3 Likert scale questions and the open question.

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

Furthermore, subjects will assess the intensity and frequency of cough and the amount of sputum production during the previous 24 hours on Likert scales as presented in **Table 6**.

Table 6 Cough Assessment Likert Scales

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

Finally, subjects will be asked to share any other important observations with the site collaborators about their coughing.

Cough Assessment will be done daily from Day -2 to Day 6 prior product use but no later than 11: 30 AM. It will also be done at Day 30 Visit, Day 60 Visit, and Day 90 Visit (second day of the respective visits) no later than 11:30 AM, irrespective of product use.

7.5 Categorical Variables

The categorical variables used in this study are shown below (**Table 7**).

Table 7:Categorical Variables Definitions

Variable	Categories
Action taken with study product due to adverse event	Product use interrupted Product use withdrawn Product use reduced None
Adverse event expectedness	No Yes
Adverse event relationship to IP	Related Not related
Adverse event relationship to Study Procedures	Related Not related
Adverse event severity	Mild Moderate Severe
Attempt to quit (based on number of days without tobacco use)	30 days ([14-44 days]) 60 days (]44-74 days]) 90 days (>74 days)
BMI (kg/m^2)	Underweight: < 18.5 Normal range: ≥ 18.5 and < 25.0 Overweight: ≥ 25.0 and < 30.0 Obese: ≥ 30.0
CO breath test level (ppm)	≤ 10 > 10
COHb level	≤ 2% > 2%
Daily CC consumption over the last 6 weeks as reported at Admission (per day).	10-19 >19
Detailed Product use Categories for CHTP 1.2 arm	Exclusive CHTP 1.2 (]95-100]%) Predominantly CHTP 1.2 ([70-95]%) Dual Mostly CHTP 1.2 (]60-70[%) Dual Balanced ([40-60]%) Dual Mostly CC (]30-40[%) Predominantly CC ([5-30]%) Exclusive CC ([0-5[%)
FTND total score	Mild: 0 – 3 Moderate: 4 – 6 Severe: 7 – 10

Table 7:Categorical Variables Definitions	
Variable	**Categories**
General Product Use Categories for CHTP 1.2 arm	CHTP 1.2 [70-100%] Dual]30-70%[CC [0-30%]
ISO tar yields	1 – 5 mg 6 – 8 mg 8– 10 mg > 10 mg
Nicotine level	<= 0.6 mg > 0.6 to <= 1 mg
Outcome of adverse event	Fatal Not recovered or not resolved Recovered or resolved Recovered or resolved with sequelae Recovering or resolving Unknown
Product Preference	CC CHTP 1.2 No Preference
Product Use **Safety** Time Periods	Period 1 ([Day 1-(Discharge from confinement)]) Period 2 ( ]Discharge from confinement – Day 30 Visit]) Period 3 ( ]Day 30 Visit- Day 60 Visit]) Period 4 ( ]Day 60 Visit -Day 90 Visit])
Product Use Time Periods	Period 1 ([Day 1-Discharge from confinement]) Period 2 ([Discharge from confinement – Day 30 Visit]) Period 3 ( ]Day 30 Visit- Day 60 Visit]) Period 4 ( ]Day 60 Visit- Day 90 Visit])
Safety Time Periods	Product Test ([Product trial – Randomization]) Randomized period: • Confinement ([Day 1-Discharge from Confinement]) • Ambulatory (]Discharge from Confinement-Discharge from Ambulatory]) • Safety Follow-up (]Discharge from Ambulatory – End of Study])
Seriousness Criteria	Fatal Life-threatening Requires hospitalization

Table 7:Categorical Variables Definitions	
Variable	**Categories**
	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 on Day 5 and in total NNAL after 90 days in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability.

Table 8 describes the expected coefficients of variation (CV) and mean ratios (MR) between CHTP 1.2 and the one 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 (**Lüdicke et al, 2016**).

Table 8 Expected Mean Ratios and Coefficients of Variation for CHTP 1.2/CC after 5 Days of exposure

	CHTP 1.2/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 = Combustible cigarettes; COHb = Carboxyhemoglobin; CV = Coefficients of variation; MHBMA = Monohydroxybutenyl mercapyuric acid; MR = Mean ratios; S-PMA = S-phenylmercapturic acid; CHTP 1.2 = Carbon Heated Tobacco Product 1.2.

Table 9 describes the expected coefficients of variation (CV) and mean ratios (MR) in total NNAL after 90 days between CHTP 1.2 and the one control arm based on a randomized, controlled, forced-switching, open-label, parallel-group, single-center study in 90 male and female adult smokers to evaluate six biomarkers of tobacco smoke exposure over a 12-week period of unrestricted smoking in the participants' normal life setting (**Frost et al. 2008**).

Table 9 Expected Mean Ratios and Coefficients of Variation for CHTP 1.2/CC after 90 Days of exposure

	CHTP 1.2/CC MR (CV)
Total NNAL	0.30 (0.60)

Abbreviations: Total NNAL = Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; MR = Mean ratio; CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CC = Combustible cigarettes; CV = Coefficient of variation.

The power to detect a reduction was computed and is presented below.

Table 10 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 1.2 arm compared to the CC arm after 5 days of exposure and total NNAL after 90 days of exposure, with a one sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and, and 120 randomized subjects in a 2:1 ratio (80 in CHTP 1.2 arm and 40 in CC arm). It is assumed that a minimal number of subjects will be excluded from the PP set in confinement for both arms and CC in ambulatory, whereas at least 50% will remain in the PP set in ambulatory for CHTP 1.2, therefore a 2:1 randomization ratio was chosen.

Table 10 Expected Power

	Reduction					
Assumptions	**50%**	**51%**	**52%**	**53%**	**54%**	**55%**
YVD-CS01-EU	94%	88%	81%	70%	56%	38%

The test-wise powers to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb on Day 5 and in total NNAL after 90 days in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU, and 120 randomized subjects in a 2:1 ratio (80 in CHTP 1.2 arm and 40 in CC arm) are described in **Table 11**.

Table 11 Test-Wise Power

Parameter	**Test-Wise Power**
COHb	96%
3-HPMA	>99%
MHBMA	>99%
S-PMA	>99%

Total NNAL	98%

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 1.2 arm compared to the CC arm after 5 days of exposure, and in the levels of total NNAL in the CHTP 1.2 arm compared to the CC arm after 90 days of exposure, using a one sided test with 2.5% type I error probability.

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

- Statistical analysis for the QSU-brief questionnaire data and the mCEQ questionnaire data will be performed including interaction terms for arm and time point to enable least square means to be calculated at each time point in order to explore the pattern of the CHTP 1.2 effect over time. The main comparison between arms will be the comparison over all of the time points.
  Reason for change:
  This analysis would capture the evolution of perception of the product and the adaptation process taking into account the subjects' repeated measurements.
- 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.
- The summary of demographics will also be performed on the FAS.
  Reason for change:
  If the safety population differs from the FAS, then a summary of the demographics for the FAS is also required.
- The categorisation of the SES questionnaire into low, moderate and high SES will not be performed.
  Reason for change:
  There is no scoring algorithm available for the Socio-Economic Status questionnaire in the study population.
- The number and percentage of subjects with clinical findings will not be tabulated by sequence for laboratory parameters.
  Reason for change:
  No sequence occurred in this study. The tabulation will be done by arm. The error is corrected in this Analysis Plan.
- The endpoint "Ratio of 8-epi-prostaglandin F2α (8-epi-PGF2α) to prostaglandin F2α (PGF2α)" will only be listed.
  Reason for change:
  During the course of the study, the most recent development of the assay to measure the 8-epi-PGF2α to PGF2α ratio showed that the ratio is not an effective endpoint for the

determination of oxidative stress. The collection of samples and the analysis for this endpoint was stopped and the results will only be listed in the Clinical Study Report.

- The definition of the Quitters population was added in section **10.7 Quitters Population**.
  Reason for change:
  The purpose of this addition was to clarify the population on which exploratory endpoint 4 will be assessed.

10 ANALYSIS POPULATIONS

The study population characteristics will be described on the Safety Population, FAS, (if different from Safety Population), and on the Per-Protocol populations for Period 1 and 4. The per-protocol populations will be the primary analysis set for biomarkers of exposure, cotinine and nicotine in plasma, CYP1A2, CYP2A6, Ames Mutagenicity test, clinical risk endpoints, FTND, mCEQ, ITUQ, Cough and QSU-brief. The Full Analysis Set will be the primary analysis set for exposure to product, compliance to randomization arm, Prochaska and SES. Exposure and questionnaires, as a secondary analysis, will be described by randomization arm and product use category using the full analysis set. If the FAS and PP population differ, the biomarkers of exposure tables will be repeated on the FAS.

Safety will be analyzed using the safety population.

10.1 Screened Population

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

10.2 Enrolled Population

The enrolled population consists of all subjects who were enrolled.

10.3 Randomized Population

The randomized population consists of all subjects who were randomized.

10.4 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.

10.5 Per Protocol Populations

The PP populations are subsets of the FAS and include, by period, all randomized subjects who fulfill key compliance criteria of the protocol in the respective period, and have no major protocol deviation impacting evaluability as defined in **Table 12** (see Section **11**"**Protocol Deviations**").

10.6 Safety Population

The safety population consists of all the subjects who had at least one exposure to CHTP 1.2, irrespective of whether or not the subject was exposed post-randomization. Subjects in the safety population will be analyzed according to actual exposure. The actual exposure differs from the exposure as randomized only for subjects who consistently used the wrong product; ie if the site had consistently administered the wrong product inadvertently.

10.7 Quitters Population

The quitters population consists of all subjects from the Full Analysis Set who had no CC, CHTP, e-cigarette or other tobacco products for at least 14 days prior to Discharge at Day 90 Visit or the date of early termination as reported in the product use diary.

If there are at least 10 subjects in any treatment group and timepoint who attempted to quit (see **Table 7**), the table with descriptive statistics will be repeated for that group. These tables will then get an additional ".1" to the table numbering and "by attempt to quit" will be added in the title. Subjects who restart any tobacco product use will not be included in this analysis. Otherwise, these data will be included in the listings only.

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 subject for the primary objectives of the study and therefore should result in the subject being excluded from the PP Population at the time of deviation.

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 categories for the major deviations may include, but are not limited to the deviations presented in **Table 12**.

Table 12: Definition of Major Protocol Deviations

Category	Description
Mis-randomization	An error in the randomization and/or product allocation process.
Product adherence	**Confinement:** Use of any nicotine or tobacco–containing product other than the assigned product, using the product distribution log. **Ambulatory:** Non-compliance in the CHTP 1.2 arm will be defined for each period. Non-compliance is based on product use reported in the product use diary for periods 2-4, as any of the following occurrences: – Use of more than 2 CC in a single day – Average product use from Day 1 through the end of the period is more than 0.5 CC per day.
Protocol violation	A deviation to the inclusion/exclusion criteria.
Procedural violation	A major deviation in the conduct of a procedure
Duration of 24 hour urine collection	Not all urine collected over 24 hours or collection period covers less than 20h or covers more than 28h for Day -2, Day -1, Day 1, Day 2, Day 3 or Day 4, Day 5/Discharge from Confinement, Day 30 Visit, Day 60 Visit or Day 90 Visit
Concomitant medication	Use of drugs which are known to affect CYP2A6 or CYP1A2 activity (except medication containing estrogen) or could interfere with clinical risk endpoints such as 11-DTX-B2..
Reporting of product use	Less than 75% of the daily product use reported in the e-diary over a period is available, or daily product use not reported over a period of more than 7 consecutive days
Visit missing	Scheduled visit not done

Subjects with violations of inclusion criteria 1, 2, 4 and 6, or of exclusion criteria 2 to 4, 15, 18 and 19 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.

Single use of more than 2 CCs on a single day would exclude all measurements within a week after the deviation. The impacted subject would be classified as non-evaluable for the objectives assessed within a week after the deviation.
Average product use higher than 0.5 CC per day from Day 1 through an evaluation timepoint would exclude all measurements at that evaluation point. The impacted subject would be classified as non-evaluable for the objectives of the study at that evaluation point.

11.2 Minor Protocol Deviations

The categories for the minor deviations may include, but are not limited to the deviations presented in **Table 13**.

Table 13: Definition of Minor Protocol Deviation Categories

Category	Description
Time deviation	Assessments not taken at the correct time or within the allowed time window (see **Table 14**)
Visit window deviation	Visits not performed within the allowed time window (see **Table 14**)
Time missing	Assessment date or time is missing
Procedural violation	A minor deviation in the conduct of a procedure
Duration of 24 hour urine collection	Urine collection period duration in [20h -23h[or]25h-28h] for Day -2, Day -1, Day 1, Day 2, Day 3 or Day 4, Day 5/Discharge from Confinement, Day 30 Visit, Day 60 Visit or Day 90 Visit
Assessment missing	Assessment is missing

11.3 Assessment Windows

Use of the randomized products in the confinement setting should take place within the 06:30 AM and 11:00 PM window. At Day 30 Visit, Day 60 Visit, and Day 90 Visit, subjects in the CHTP 1.2 and CC arms will be allowed to use their assigned product from the time of check-in until 11:00 PM. On the second day of Day 30 Visit and Day 60 Visit, product use will be allowed from 06:30 AM.

The assessment windows are shown in **Table 14**.

Table 14: Assessment Windows

Assessment	Nominal Time point(s)	Window
24 h urine sample	Day -2 to Day 6	Day -2:prior to 11:30 AM on Day -2 (start) to after 24 hours ±1 hour later on Day -1 (end). The end of the 24-hour urine should be prior to smoking the first CC. From Day -1 onwards until Day 6: start after the end of 24-hour urine collection of the previous day (after 24 hours ±1 hour). The end of the 24-hour urine should be prior to smoking the first CC in the

Table 14: Assessment Windows

Assessment	Nominal Time point(s)	Window
		CC arm and prior to use of the first CHTP 1.2 in the CHTP 1.2 arm.
	Day 30 Visit, Day 60 Visit and Day 90 Visit	Start at 09:00 ± 30 minutes (after bladder void) until 24-hours ±1 hour later.
Spirometry	Screening	spirometry without bronchodilator: at least 1 hour after having stopped smoking and prior to spirometry with bronchodilator spirometry with bronchodilator performed 15-30 minutes post administration of salbutamol
	Day 6 and Day 90 Visit	spirometry will be performed prior to product use (CC or CHTP 1.2). spirometry post-bronchodilator performed 15-30 minutes post administration of salbutamol Day 6: 06:29 AM ± 1.5h Day 91: prior to 11:30 AM
CYP1A2 activity	Day -1, Day 5 and Day 90 Visit	6 hours after intake of cup of coffee ± 15 min
CYP2A6 activity	Day -3,Day 6 and Day 90 Visit	Prior to smoking / product use Day -3 and Day 90 Visit (Day 91): prior to 11:30 AM Day 6: 06:29 AM ± 1.5h
CO breath test	Day -2 to Day 5	in the evening around 08:00 PM ± 1.5 hour in conjunction (i.e., within 30 minutes) with COHb tests.
	Day -3, Day 30 Visit, Day 60 Visit and Day 90 Visit	First day of the respective visits; irrespective of time of product use
Assessment of Cough	Day -2 to 6	To be done prior to product use but not later than 11:30 AM
	Day 30 Visit, Day 60 Visit and Day 90 Visit	Second day of the respective visits; prior to 11:30 AM; irrespective of time of product use
Nicotine and cotinine in plasma	Day -1 to Day 6	Day -1 to Day 5: between 08:00 PM ± 1.5 hour. Day 6: between 06:29 AM ± 1.5h.

Table 14: Assessment Windows

Assessment	Nominal Time point(s)	Window
	Day 30 Visit, Day 60 Visit and Day 90 Visit	Day 30 Visit, Day 60 Visit, and Day 90 Visit (first day of the respective visits): irrespective of the time of product use.
COHb blood sampling	Day -2 to Day 5, Day 30 Visit, 3 and 4	From Day -2 to Day 5: in the evening around 08:00 PM ± 1.5 hour. At Day 30 Visit, Day 60 Visit, and Day 90 Visit (first day of the respective visits): irrespective of the time of product use.
mCEQ, QSU, ITUQ, Prochaska, FTND (as applicable)	Day -2 to Day 5, Day 30 Visit, Day 60 Visit and Day 90 Visit	08:00-11:00 PM
Clinical laboratory parameters, cardiovascular/oxidative stress clinical risk endpoints in blood (as applicable)	Screening, Day -1, Day 5, Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit	Prior to 11:30 AM on Day 1, Day 5 and Day 30 Visit, Day 60 Visit and Day 90 Visit (second day of the respective visit) Day 6: 06:29 AM ± 1.5h

11.4 Invalid data

Data will be reviewed prior to locking the database. Assessments of endpoints will be reviewed for their potential invalidity. Examples of invalid assessments are:

- If the duration of urinary collection at a given timepoint is less than 20 hours or more than 28 hours, the urinary BoExp and urinary clinical risk endpoints at this timepoint would be considered invalid and not be considered in any analysis.
- CYP1A2, CYP2A6 or 11-DTX-B2 assessments within less than 5 $t_{1/2}$ after a medication with an impact on the CYP1A2, CYP2A6 or 11-DTX-B2 metabolism will be considered invalid and not be considered in any analysis.

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 arm and subject and timepoint (if applicable), unless otherwise stated. Summary statistics and statistical analyses will only be presented for data where detailed in this SAP. All unscheduled assessments will be included in the listings.

The protocol specifies that the assumptions of the analysis of variance model will be tested. The distribution of the data will be visually checked for normality or log-normality by means of histograms. Markedly non-(log)normally distributed data will be transformed or analyzed by appropriate non-parametric methods. For all endpoints, the assumed distribution is mentioned in the SAP.

For log-transformed endpoints, 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 arm along with the reduction (i.e: 100% - ratio of CHTP 1.2 : CC (%)) and 95% CI will be presented in the tables. For naturally distributed data, the obtained LS Means for each arm along with the difference between these and 95% CI will be presented in the tables.

For data summarized on the log scale (or data summarized in its natural scale and for which a log transform was applied in an attempt to get normality), markedly non-lognormally distributed parameters will be analyzed with bootstrapping the log-transformed data using the SAS PROC SURVEYSELECT procedure. The seed to be used in any analysis will be contained in the SAS output and will be different for each analysis.

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).
3. Product use category: CHTP 1.2, Dual or CC in the CHTP 1.2 arm (see **Table 7**)

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, arithmetic mean 95% CI, median, first and third quartiles, minimum, maximum, and number of BLOQ values. For log-normally distributed data, the geometric mean, geometric mean 95% CI, and geometric CV will additionally be presented. For post-baseline non-transformed endpoints, the change will be shown; for post-baseline transformed endpoints, the percent change will be shown; unless otherwise specified.

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. The actual exposure differs from the exposure as randomized only for subjects who consistently used the wrong product; ie if the site had consistently administered the wrong product inadvertently. 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 15**):

Table 15: Product Labels		
Product	**Format used in TFLs**	**Order in TFLs**
Carbon Heated Tobacco Product 1.2	CHTP 1.2	1
Combustible cigarette(s)	CC	2
Exposed not Randomized	Exposed not Randomized	3

The following stratification labels (**Table 16**) for the TFLs will be used:

Table 16: Stratification Labels	
Stratification Factor	**Definition**
Sex	male
	female
Daily CC consumption (per day)	<10[1]
	10-19
	>19
Product use category.	CHTP 1.2 Arm:
	CHTP1.2 [70-100%]
	Dual]30-70%[
	CC [0-30%]

[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 17**) for statistical analyses/presentations will be used:

Table 17: Definition of terms for the statistical analysis	
Term	**Definition**
Baseline Value	The last valid assessment at the last available time point prior to first product use in the Exposure Period.

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 laboratory parameters:

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

For daily product use data:

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

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

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

For missing or partial dates:

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

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

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

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

AEs missing relatedness or severity:

AEs missing relatedness or severity assessment will be displayed in the AE tables as per the rule described for incidence and prevalence of AEs in **12.5.4.2.1 "All Adverse Events"**.

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 have no subject for data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

For categories of summaries that have <4 subjects, only the number of subjects and the minimum and maximum will be shown.

12.1.6 Handling of Unplanned Data

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

12.1.7 Tabulation of the Per Protocol Populations

Per product use period, there will be one per protocol population. In the tables per period on the PP population, each period will show its corresponding PP population, and the baseline will be repeated per PP population. As for a repeated measurements model, each period will include its own PP population and the value for any subject in the PP of that period would be used. In the tables that are not by period, the table will be repeated for each PP population.

12.1.8 Multiple Comparisons / Multiplicity

Unless stated otherwise, all statistical tests will conducted using a one-sided test with 2.5% type I error probability, and all quoted confidence intervals (CIs) will be two-sided 95% CIs.

The primary endpoints will be tested using a closed testing procedure to preserve the overall alpha level by simultaneously testing the endpoints at the one-sided 2.5% type I error probability (**EMEA Points to consider on multiplicity issues in clinical trials**). This implies that statistical significance is required for all primary endpoints in order to be able to make confirmatory claims about any of the endpoints.

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 confinement, period 2, 3 and 4 and safety follow-up, and discontinued (if applicable discontinued subject that never used their allocated products will be identified) (Table 15.2.1.1).

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 screen failure / discontinuation will also be summarized separately (Table 15.2.1.2.1 and Table 15.2.1.2.2). Supportive listings will be provided (Listing 15.3.1.7).

The number and percent of randomized subjects with protocol deviations and the number of protocol deviations will be summarized by arm, broken down by main deviation category (major/minor) sub-categories and evaluability (Table 15.2.1.3.1). Subjects will be counted once per deviation category and per product use period, and can be counted for more than one deviation category. The number and percent of randomized subjects per study analysis population and reasons for exclusion will be summarized by arm (Table 15.2.1.3.2).

Supportive listings will be provided, including any additional comments for tests that are not performed to be included on the listings of individual data (Listing 15.3.1.10).

12.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population, FAS and PP for period 1 and 4 (Table 15.2.1.4.1, Table 15.2.1.4.2 and Table 15.2.1.4.3 respectively), and listed for all screened subjects (Listing 15.3.1.6).

The demographic variables age, sex, race, waist circumference, body weight, height and BMI, CC Nicotine level at Admission (mg), CC ISO CO level at Admission (mg), and CC ISO tar level at Admission (mg) will be summarized by exposure, and by sex, CC consumption and Product use category (Table 15.2.1.4.2.X and Table 15.2.1.4.3.X).

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

12.3.1 Socio-Economic Status (SES)

SES data will be listed as part of the demographics and baseline characteristics (Section 12.3) (Listing 15.3.1.9).

12.3.2 Current Cigarette Brand and Smoking Characteristics

The following smoking characteristics at Admission (Day -3) 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), ISO CO level (continuous), 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 Screening and Admission (Day -3) will be summarized (Table 15.2.1.5) and listed by arm for the FAS. This will include brand name(s) and ISO nicotine, tar, and CO yields. Data at screening will be listed only (Listing 15.3.1.2).

Smoking habits/history, including whether subjects have smoked for at least the last ten years, number of years smoked, how many cigarettes per day the subject has smoked over the last 6 weeks (and how much were non-menthol) and since the subject started smoking; whether the subject ever used nicotine-containing products other than commercially available non-menthol/menthol CC; and the average use of e-cigarettes over the last year, and product preference will be listed by product at Screening and Admission (Day -3) where applicable (Listing 15.3.1.3 and Listing 15.3.1.4).

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 arm, System Organ Class (SOC) and Preferred Term (PT) within SOC (Listing 15.3.1.8).

Medical History will be summarized by arm, SOC and PT for the Safety Population (Table 15.2.1.6).

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 arm, SOC and PT within SOC (Listing 15.3.1.8).

Concomitant disease will be summarized by arm, SOC and PT for the Safety Population (Table 15.2.1.7).

Partial dates will not be imputed, but assumptions will be made as follows to assign to either medical history or concomitant diseases (see section **12.1.5 Handling of Dropouts or Missing Data (including outside the limits of quantification)**).

12.3.4 Other Data

Other data collected at Screening and/or Admission will be listed by arm (Listing 15.3.1.5, Listing 15.3.6.6 and Listing 15.3.1.4). These data are as follows:

- Cotinine urine test
- Serum and Urine pregnancy test
- Chest x-ray
- Urine drug screen
- Serology
- Alcohol breath test
- Prior and concomitant medication
- Willingness to use CHTP 1.2

12.4 Extent of Exposure (Product Consumption)

Details of the product test and of daily product use will be listed and summarized (Table 15.2.2.X and Listing 15.3.2.1). For the FAS, the summaries will be repeated per Product Use Category for the ambulatory period and per Product Preference for the confinement and ambulatory period (Table 15.2.2.3.X):

- The number of uses of CHTP 1.2 at product test will be tabulated per arm.

- During the confinement period: descriptive statistics of the number of uses on a day-by-day basis per product.

- During the ambulatory period: descriptive statistics per product period of the average and the maximum daily usage per product.

12.5 Planned Statistical Analyses

12.5.1 Primary Analyses

The per-protocol population for period 1 and period 4 will be the primary analysis set for biomarkers of exposure. See also **section 12.1.7**.

12.5.1.1 Primary endpoints

COHb in blood, and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA, and total NNAL will be summarized on the log-scale as detailed in Section **12.1.3** "**Descriptive Statistics**". Distributions will be tested for log-normality and appropriate non-parametric methods will be used in case of non-lognormally distributed data as described in **12.1 General Considerations**.

The values and percent changes from baseline in the concentration adjusted for creatinine of MHBMA, 3-HPMA, S-PMA and total NNAL will be listed and summarized along with the COHb concentrations and percent changes from baseline (Tables 15.2.3.3-7.1, 15.2.3.3-7.2 and Listing 15.3.3.1). This will also be summarized by sex, by average cigarette consumption over the previous 6 weeks prior to admission and by product use category (Tables 15.2.3.3-7.1.1, 15.2.3.3-7.1.2 and 15.2.3.3-7.1.3).

The log-transformed data will be analyzed by means of an ANCOVA (on Day 5 for COHb, MHBMA, 3-HPMA and S-PMA and Day 90 Visit for total NNAL) using arm as covariate adjusting for sex and average cigarette consumption over the previous 6 weeks prior to admission, and log-transformed baseline value of endpoint.

The SAS code to be used for COHb in blood, and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA on Day 5 and total NNAL adjusted for creatinine at Day 90 Visit is shown below:

```
Proc mixed data=_data_;
Class arm sex cigarette_cons;
Model log (Value) = log (baseline) sex cigarette_cons  arm;
Lsmeans arm / 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 arm along with the reduction (i.e: 100% - ratio of CHTP 1.2 : CC (%)) and 95% CI will be presented in the tables (Table 15.2.3.1).

In addition line graphs will be produced for arm geometric means (and 95% CI) over all timepoints for COHb in blood, and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA, S-PMA and total NNAL (Figure 15.1.1.1-5).

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, the percent change in quantity excreted over 24 hours and the values for creatinine for the 24h urine (Listing 15.3.3.1).

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% (Listing 15.3.3.1).

If applicable, the tables with descriptive statistics will be repeated for the group of subjects who attempt to quit (see section **"10.7 Quitters Population"**)

12.5.1.2 Confirmatory Hypothesis

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 for COHb, MHBMA, 3-HPMA and S-PMA and at Day 90 Visit for total NNAL for CHTP 1.2 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 COHb, MHBMA, 3-HPMA and S-PMA levels on Day 5 and total NNAL levels at Day 90 Visit for CHTP 1.2 and CC respectively.

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 -3 to Day 5, Day 30 Visit, Day 60 Visit and Day 90 Visit.

Descriptive statistics summarized by arm will be produced separately for all timepoints for all visits applicable for exhaled CO. Exhaled CO will be summarized on the natural scale as detailed in Section **12.1.3** "**Descriptive Statistics**". Distribution will be tested for normality and appropriate non-parametric methods will be used in case of non-normally distributed data as described in **12.1 General Considerations**.

Actual values and changes from baseline in levels of exhaled CO will be listed and summarized (Table 15.2.4.2.X and Listing 15.3.3.1). In addition line graphs will be produced for arithmetic means (and 95% CI) per randomization arm over all timepoints (Figure 15.1.2.5).

An ANCOVA model on exhaled CO (Day 5 and Day 90 Visit) will be used with terms for the baseline value, sex, average cigarette consumption over the previous 6 weeks prior to Admission and arm.The LS means on Day 5 and Day 90 for each arm along with the difference (CHTP 1.2 - CC) and 95% confidence interval (CI) will be presented in the tables (Table 15.2.4.1).

The statistical model and SAS code for the analysis of exhaled CO on Day 5 and at Day 90 Visit and COHb at Day 90 Visit will be the same as described in Section **12.5.1.1 "Primary endpoints"**; except that there will be no log transformation of the data and back-transformation of the LS Means estimates of the difference.

If applicable, the table with descriptive statistics will be repeated for the group of subjects who attempt to quit (see section **"10.7 Quitters Population"**)

12.5.2.1.2 Urinary Biomarkers of Exposure

The Urinary Biomarkers of Exposure assessed as secondary endpoints are total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, Total 3-OH-B[a]P, HMPMA assessed at Day 5 and Day 90 Visit, MHBMA, 3-HPMA and S-PMA assessed at Day 90 Visit and Total NNAL assessed at Day 5.

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. These endpoints will be log-transformed.

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 (Table 15.2.4.3-12.1 and 15.2.4.3-12.2 and Listing 15.3.3.1). In addition line graphs will be produced for arm geometric means (and 95% CI) over all timepoints (Figure 15.1.2.1-25).

The analysis will compare the log-transformed urinary concentrations adjusted for creatinine and the quantity excreted over 24-hours between the CHTP 1.2 and CC arms on Day 5 and Day 90 Visit for 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, Total 3-OH-B[a]P, HMPMA.

The analysis will also compare the log-transformed urinary concentrations adjusted for creatinine and the quantity excreted over 24-hours between the CHTP 1.2 and CC arms for MHBMA, 3-HPMA, S-PMA at Day 90 Visit and for total NNAL at Day 5 as well as the quantity excreted over 24-hours between the arms for MHBMA, 3-HPMA and S-PMA at Day 5 and for total NNAL at Day 90 Visit.

The statistical model and SAS code will be the same as described in Section **12.5.1.1 "Primary endpoints"**. Note that for the analyses at Day 90 Visit, the p-value will only be shown if the one-sided p-value at Day 5 was significant (i.e. < 0.025). The geometric LS means for each arm along with the reduction (i.e: 100% - ratio of CHTP 1.2 : CC (%)) and 95% CI will be presented in the tables (Table 15.2.3.2, Table 15.2.4.1)

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 arm along with the reduction (i.e: 100% - ratio of CHTP 1.2 : CC (%)) and 95% CI will be presented in the tables (Table 15.2.4.1).

12.5.2.1.3 NEQ

NEQ will be expressed as concentrations adjusted for creatinine and as the quantity excreted over 24 hours. It will be assumed that NEQ is log-normally distributed.

The values and percent changes for NEQ in the quantity excreted over 24-hours and the concentration adjusted for creatinine will be listed and summarized (Table 15.2.4.13.X and Listing 15.3.3.1). In addition line graphs will be produced for arm geometric means (and 95% CI) over all timepoints (Figure 15.1.2.26 and 15.1.2.27).

The analysis will compare the log-transformed NEQ between the CHTP 1.2 and CC arms on Day 5 and Day 90 Visit. The statistical model and SAS code will be the same as described in Section **12.5.1.1 "Primary endpoints"** (Table 15.2.4.1).

In addition, a repeated measures mixed model on the log-transformed NEQ will be used with terms for log-transformed baseline, sex, average daily CC consumption over the last 6 weeks as reported during admission, arm, timepoint, and the interaction between arm 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_ method=REML;
Class arm sex cigarette_cons time_point_cat subject period;
Model log(NEQ) = log(base) sex period cigarette_cons arm
arm*time_point time_point;
Repeated time_point_cat / subject=subject type=un;
Lsmean arm / diff 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 arm along with the reduction (i.e: 100% - ratio of CHTP 1.2 : CC (%)) and 95% CI will be presented in Table 15.2.4.14. This will be done for all individual timepoints. If the interaction term is present in the model, the reduction will also be shown for the individual timepoints.

12.5.2.2 Nicotine and Cotinine Concentrations

It is assumed that Nicotine and Cotinine concentrations are log-normally distributed.

The descriptive analysis will be the same as described in Section **12.5.1.1 "Primary endpoints"**.

The percent change from baseline will be calculated. The concentrations of nicotine and cotinine will be listed and summarized along with this change (Table 15.2.4.15 and Listing 15.3.4.1). Line graphs of the nicotine and cotinine concentration profiles across all study days showing geometric mean and 95% CI will also be produced (Figure 15.1.2.28).

Nicotine and cotinine values will also be analyzed in a repeated measures mixed model on the log-transformed values, as described in section "**12.5.2.1.3 NEQ**" (Table 15.2.4.16).

12.5.2.3 CYP1A2 Activity

It is assumed that CYP1A2 Activity is normally distributed.

Descriptive statistics of the values and change from baseline and supportive listings will be provided (Table 15.2.4.17 and Listing 15.3.3.1).

The analysis will compare the Day 5 and Day 90 Visit values between the CHTP 1.2 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 admission and arm. The SAS code will be the same as described in Section**12.5.1.1 "Primary endpoints"**; but then without a log-transformation.

The least squares (LS) means and estimate of the difference along with it's 95% CI will be presented in the tables (Table 15.2.4.18).

12.5.2.4 Spirometry

Spirometry parameters assessed during the study include:

- Measured forced expiratory volume in 1 second (FEV_1)
- Measured forced vital capacity (FVC)
- FEV1/FVC
- Percent of predicted FEV1 (% pred)
- Percent of predicted FVC (% pred)
- Measured FEF 25 - 75
- Measurement interpretation (categories: normal, abnormal, abnormal clinically significant)

The above data are collected at Screening, Day 6, and Day 90 Visit. At Screening, data are collected at least one hour after having stopped smoking. On Day 6 and Day 90 Visit, spirometry has to be done prior to smoking.

It is assumed that these parameters are normally distributed.

Spirometry data values and normal/abnormal will be listed by arm and study day (Listing 15.3.4.3). 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), FEV_1/FVC, FEF (measured) at baseline, on Day 6 and at Day 90 Visit by arm, and overall for the safety population and for the PP population. Spirometry data will be summarized together with changes from baseline for data with and without bronchodilator (Table 15.2.4.19.x). The number and percentage of subjects with normal/abnormal/abnormal clinically significant results will be presented in Table 15.2.4.20.X.

For the PP population, the analysis will compare the Day 6 and Day 90 Visit values between the CHTP 1.2 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 admission and arm. The SAS code will be the same as described in Section **12.5.1.1 "Primary endpoints"**; but then without a log-transformation.

The least squares (LS) means and estimate of the difference along with its 95% CI will be presented in the tables. The LS means for each arm along with the difference and 95% CI will be presented in the table (Table 15.2.4.21).

12.5.2.5 Assessment of Cough

Cough questionnaire is assessed on a daily basis from Day -2 to Day 6, at Day 30 Visit, Day 60 Visit and Day 90 Visit. Questionnaire details are reported in Section **7.4.7** "**Cough Assessment**".

The number and % of subjects reporting cough will be summarized over the study by study arm for the safety and PP population and by product use pattern categories for the Safety population. 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 summarized over the study by study arm for all subjects who filled in the questionnaire and reported cough (Table 15.2.4.22.X). If a subject has answered question more than once then the most severe intensity/frequency/sputum production is presented for the "over the study" tables. No assumptions will be made in case of missing intensity/frequency/sputum production. The number and % of subjects reporting cough, 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 and by product use pattern categories (Table 15.2.4.23.X and Table 15.2.4.24.X) for all subjects who filled in the questionnaire and reported cough. The answers to the open question(s) related to any other important observation will be listed (Listing 15.3.4.4).

In addition, a GEE model will be used to evaluate the differences between proportions (with 2-sided p-values) and 95% CI for the need to cough between CHTP 1.2-use and CC-use at

V2, V3 and V4 in the per protocol population and in the safety population (Table 15.2.4.26.X). The model will include terms for visit, baseline level and its interaction with visit, sex, and product use pattern category and its interaction with visit. The point estimate and 95% CI of proportions and the Odds Ratios (with 2-sided p-values) will also be produced for CHTP 1.2 (CHTP 1.2 arm) versus CC (CC arm) and for CHTP 1.2 Dual-use (CHTP 1.2 arm) versus CC-use (CC arm). The interaction term will be removed if p > 0.1.

The SAS code to be used is shown below:

```
proc glimmix data = _data_ ;
  class trtan avisit sex usubjid;
  model aval = base base*visit pattern avisit sex
trtan*pattern/dist = binomial link=logit solution;
  random _residual_/subject=usubjid type = un;
  lsmeans trtan*avisit ;
run;
```

For the confinement period, a similar model will be run, replacing the product use category with the treatment arm (Table 15.2.4.25.X).

12.5.2.6 Cardiovascular Risk Endpoints

The following cardiovascular risk endpoints will be assessed:

- Systolic and Diastolic Blood Pressure at baseline, Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit.
- High sensitive C-reactive protein (hs-CRP), blood glucose, myeloperoxidase (MPO), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) in serum at Baseline, Day 30 Visit, Day 60 Visit, and Day 90 Visit
- Fibrinogen, homocysteine in plasma at baseline, Day 30 Visit, Day 60 Visit, and Day 90 Visit
- Hemoglobin A1c (HbA1c) in blood at Day -1, and Day 90 Visit
- Apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) in serum at baseline, and Day 90 Visit
- Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum at baseline, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit
- White blood cell (WBC) and platelet counts in blood at baseline, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit
- 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine at baseline, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine)
- Body Weight and Waist Circumference at baseline and Day 90 Visit.

It is assumed that the following cardiovascular parameters can be analyzed in natural scale: MPO, Apo A1, Apo B, LDL-C, HbA1c, WBC count, Systolic and Diastolic Blood Pressure, weight, and waist circumference.

It is assumed that the following cardiovascular parameters can be analyzed in the logarithmic scale: hs-CRP, blood glucose, TG, TC, fibrinogen, homocysteine, sICAM-1, platelets and 11-DTX-B2.

These clinical risk endpoints will be summarized and listed by arm, subject, parameter and time point, together with numerical changes or percent changes (as applicable; see section "**12.1.3 Descriptive Statistics**") from baseline (Listing 15.3.4.5). The number and percentage of subjects with normal results, high/low results and abnormal clinical result (as defined by PI comment) and with shift in normality or toxicity if applicable will be tabulated.

The actual values, along with the change from baseline for MPO, Apo A1, Apo B, LDL-C, HbA1c, WBC, Systolic and Diastolic Blood Pressure, weight, and waist circumference will be summarized (Table 15.2.4.26).

The actual values, along with the percent change from baseline for glucose, hs-CRP, TG, TC, homocysteine, fibrinogen, sICAM-1, platelets, 11-DTX-B2 will be summarized (Table 15.2.4.27).

The profiles of the means (geometric for parameters analyzed in logarithmic scale and arithmetic for parameters analysed in natural scale) per time point will be produced for all endpoints except HbA1c, Apo A1, Apo B, weight and waist circumference which are only assessed at baseline and Day 90 Visit (Figure 15.1.2.29–46).

For all endpoints, an ANCOVA model will be used on Day 5 and on the Day 90 Visit (as applicable). The SAS code will be the same as described in Section **12.5.1.1 "Primary endpoints"**; except that there will only be a log transformation of the endpoints as specified above. For HbA1c, Apo A1, Apo B, waist circumference and body weight; the analysis will compare the Day 90 Visit values.

As applicable, geometric LS means for each arm along with the % reduction (100% - CHTP 1.2 : CC Ratio (%)) for hs-CRP, blood glucose, TG, TC, fibrinogen, homocysteine, sICAM-1, platelets and 11-DTX-B2 or the arithmetic LS means along with the difference (CHTP 1.2 - CC) for the other endpoints; per timepoint with 95% CI will be presented in the table. (Table 15.2.4.28).

All figures, summaries and analyses will be performed on the Per Protocol Populations.

If applicable, the tables with descriptive statistics will be repeated for the group of subjects who attempt to quit (see section **"10.7 Quitters Population"**).

12.5.2.7 Risk Endpoints related to Oxidative Stress

The following risk endpoints related to oxidative stress will be assessed:

- Epi-prostaglandin F2α (8-epi-PGF2α) in 24-hour urine at baseline, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine)
- Ratio of 8-epi-prostaglandin F2α (8-epi-PGF2α) to prostaglandin F2α (PGF2α) in plasma at baseline, Day 5 and Day 90 Visit (results only listed).
- 8-Hydroxy-2'-deoxyguanosine (8-OHdG) in 24-hour urine at baseline, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine)
- Total anti-oxidant capacity (TAC) in serum at baseline, Day 5 and Day 90 Visit.

It is assumed that all oxidative stress parameters are log-normally distributed.
These clinical risk endpoints will be summarized and listed by arm, subject, parameter and time point, together with changes from baseline (Listing 15.3.4.6).

The actual values, along with the percent change from baseline will be summarized (Table 15.2.4.29).

The profiles of geometric means per time point will be produced for all endpoints (Figure 15.1.2.47-49).

The analysis will compare the Day 90 Visit log-transformed values between the CHTP 1.2 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 admission, log-transformed baseline value and arm. The SAS code will be the same as described in Section **12.5.1.1 "Primary endpoints"**.

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 arm along with the reduction (i.e: 100% - ratio of CHTP 1.2 : CC (%)) and 95% CI will be presented (Table 15.2.4.30).

All figures, summaries and analyses will be performed on the Per Protocol Populations.

If applicable, the tables with descriptive statistics will be repeated for the group of subjects who attempt to quit (see section **"10.7 Quitters Population"**).

12.5.3 Exploratory Analysis

12.5.3.1 Questionnaires

If feasible, all questionnaire endpoints will be analyzed in natural scale

12.5.3.1.1 Urge-to-Smoke Questionnaire of Smoking Urges Brief

All summaries, profiles and analysis will be presented for the CHTP 1.2 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 (Table 15.2.5.1). The answers to the individual questions, along with the domain scores, total scores and changes from baseline will be listed (Listing 15.3.5.1).

The profiles of the arithmetic means and LS Mean differences per timepoint for the total score and two domain scores will be produced (Figure 15.1.3.1 and Figure 15.1.3.2).

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

The SAS code will be the same as the repeated measures model described in Section **"12.5.1.1 Primary endpoints"**.

LS means for each arm along with the difference (CHTP 1.2 - CC) with 95% CI will be presented in table 15.2.5.2.

All figures, summaries and analyses will be performed on the Per Protocol Populations.

12.5.3.1.2 Modified Cigarette Evaluation Questionnaire

All summaries, profiles and analysis will be presented for the CHTP 1.2 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 (Table 15.2.5.3). The answers to the individual questions, along with the domain scores and changes from baseline will be listed (Listing 15.3.5.2).

The analysis will compare each post baseline timepoint in the subscales. A repeated measures mixed model will be used with terms for baseline mCEQ score, sex, average daily CC consumption over the last 6 weeks as reported during admission, arm, time-point, and the interaction between arm and time-point. The interaction term will be removed if $p > 0.1$.

The SAS code will be the same as described in Section **12.5.2.1.3 "NEQ"**.

LS means for each arm along with the difference (CHTP 1.2 - CC) with 95% CI will be presented in the table (Table 15.2.5.4).

The profiles of the change in arithmetic means and LS Means per time point for the five subcale scores will be produced (Figure 15.1.3.3 and Figure 15.1.3.4).

All figures, summaries and analyses will be performed on the Per Protocol Populations.

12.5.3.1.3 The Intent to Use Questionnaire (ITUQ)

The summaries will be presented for the CHTP 1.2 arm.

The answers to the individual questions will be tabulated (Table 15.2.5.5).and listed (Listing 15.3.5.3).

12.5.3.1.4 Fagerström Test for Nicotine Dependence (FTND)

All summaries, profiles and analysis will be presented for the CHTP 1.2 and CC arm.

The total score, along with the change from baseline will be summarized by means of descriptive statistics and a tabulation of the categorized total scores (Table 15.2.5.6). The answers to the individual questions, along with the total scores and changes from baseline will be listed (Listing 15.3.5.4).

The analysis will compare the Day 90 Visit values between the CHTP 1.2 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 admission and arm. The SAS code will be the same as described in Section **"12.5.1.1 Primary endpoints"**; except that there will be no log transformation of the data (Table 15.2.5.7).

LS means for each arm along with the difference (CHTP 1.2 - CC) and 95% CI will be presented in the tables.

12.5.3.1.5 Prochaska "State of Change" Questionnaire: Intention to Quit Smoking

The stages of change will be cross-tabulated (screening vs Day 90 Visit) per arm (Table 15.2.5.8) and listed (Listing 15.3.5.5). The cross-tabulation will also be created per product use category (Table 15.2.5.8.1).

12.5.3.2 CYP2A6 Activity

If feasible, CYP2A6 will be analyzed in natural scale.

Descriptive statistics of the values and change from baseline on Day 6 and Day 90 Visit (Table 15.2.5.9) and supportive listings will be provided (Listing 15.3.5.6).

The analysis will compare the Day 6 and Day 90 Visit values between the CHTP 1.2 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 admission and arm (Table 15.2.5.10).

The SAS code will be the same as described in Section **"12.5.1.1 Primary endpoints"**.

LS means for each arm along with the difference (CHTP 1.2 - CC) and 95% CI will be presented in the tables.

12.5.3.3 Ames Mutagenicity Test

It is assumed that Ames Mutagenicity Test is log-normally distributed.

The 24 hour urine collection for the Ames mutagenicity test will be on Day -1, Day 5 and Day 90 Visit.

Descriptive statistics of the values and change from baseline of the YG1024+S9 mutagenicity will be provided (Table 15.2.5.11), along with listings (Listing 15.3.3.1).

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

All safety data collected during the study will be provided in listings by randomization arm, subject and product use pattern category defined over the 3-month period. The safety time periods are defined in table **Table 7: Categorical Variables Definitions"**.

All summaries for safety parameters will be conducted on the Safety Population. Unless otherwise specified, summaries will be produced overall by randomization arm and by product use pattern categories

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. 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 randomized" as a column header.

Partial dates will not be imputed, but assumptions will be made as follows to assign to product-emergent or not (see section **12.1.5 Handling of Dropouts or Missing Data (including outside the limits of quantification)**).

12.5.4.2 Adverse Events

12.5.4.2.1 All Adverse Events

All AE tables will be presented by randomization arm.

In general, AE summary tables reporting the number of events and the number and percentage of subjects reporting at least one AE will be produced by study arm and by product use pattern categories for the Pre-Randomization and Randomized periods.

In addition, AE data during the Randomized period will also be presented stratified by Confinement, Ambulatory, Safety Follow-up and overall (for the randomized period).

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 for the incidence of that AE (e.g., by severity = severe, by relatedness = related to IP). If across all AEs, subject has more than one AE, subjects will be counted only once with the worst occurrence of his/her AEs. Missing attributes for seriousness are diplayed as serious and missing severity as severe. The number of missing attributes are also displayed. Missing attributes for both relationship and study procedures are displayed as related to IP and not related to study procedures. For the prevalence of AEs, the breakdown by each severity and relatedness will be shown.

A general summary table of AEs (Table 15.2.6.1) 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 1.2 / 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 (Table 15.2.6.2 and Table 15.2.6.2.1).
- The number of events and the number and percentage of subjects with at least one AE related to product exposure and expectedness (Table 15.2.6.4).
- The number of events and the number and percentage of subjects with at least one AE leading to product discontinuation (Table 15.2.6.5).
- The number of events and the number and percentage of subjects with at least one AE leading to study discontinuation (Table 15.2.6.6).
- The number of events and the number and percentage of subjects with at least one AE related to study procedure (Table 15.2.6.7).
- The number of events and the number and percentage of subjects with at least one AE by severity (mild, moderate, severe) (Table 15.2.6.8).

The number of events and the number and percentage of subjects reporting at least one AE, by Product Use Safety Time Periods (defined in section 7.4; Table 15.2.6.3).

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**") (Table 15.2.6.9), 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) (Table 15.2.6.10).

SAEs will also be listed in a separate listing by arm (Listing 15.3.6.1.2).

12.5.4.2.3 Adverse Events Leading to Discontinuation

Summaries will be presented for AEs leading to study discontinuation, by arm as described in Section **12.5.4.2** "**Adverse Events**" (Table 15.2.6.6).

AEs leading to withdrawal will also be listed in a separate listing by arm (Listing 15.3.6.1.3).

12.5.4.2.4 Laboratory Abnormalities

Laboratory abnormality data will be listed ordered by arm, subject, parameter and time point (Listing 15.3.6.2 - Listing 15.3.6.4). Details related to the toxicity grading of laboratory abnormalities are available in Section 12.5.4.3.

12.5.4.3 Clinical Laboratory Evaluation

Table 18 below lists the hematology, clinical chemistry and urine analysis parameters to be assessed in this study.

Table 18: 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 (Table 15.2.6.11-13) and listed by arm, subject and parameter, at Screening and Day -1 for the Pre-Randomization period and at Day 6, Day

30 Visit, Day 60 Visit and Day 90 Visit for the Randomized period, together with numerical changes from baseline (Listing 15.3.6.2 - Listing 15.3.6.4). The number and percentage of subjects with normal results, high/low results, abnormal clinical result (as defined by PI comment) and with shift in normality and shift in toxicity grading from baseline 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, the CTCAE grade and the shift in normality and shift in toxicity. Only CTCAE grades of 1 or more will be presented.

12.5.4.4 CHTP 1.2 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 (Table 15.2.6.14), 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 ([redacted]).
- Number of product quality complaints.

Product quality complaints will be listed by arm (Listing 15.3.6.5). Data collected during Screening will be listed but not summarized.

12.5.4.5 Physical Findings, Vital Signs 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 arm 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 (Listing 15.3.6.6). Partial dates will not be imputed, but assumptions will be made as follows to assign to either prior or concomitant (see section **12.1.5 Handling of Dropouts or Missing Data (including outside the limits of quantification)**).

Prior and concomitant medications will be listed by arm. Prior and concomitant medications will be summarized for the Safety Population showing the number and percentage of subjects who used the medication at least once by arm and by ATC 1st and 2nd levels and preferred drug name (Table 15.2.6.15.1 - Table 15.2.6.16.2). Listings will display original dates (no imputation).

12.5.4.5.2 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate measured during the study will be listed by study visit and by arm (Listing 15.3.6.7). Assessment after baseline will include change from baseline.

Descriptive statistics on actual values and change from baseline will be presented for systolic and diastolic blood pressure, pulse rate and respiratory rate on every subsequent day of the confinement period and at Day 30 Visit, Day 60 Visit, and Day 90 Visit during the ambulatory period, by arm (Table 15.2.6.17).

12.5.4.5.3 Body Weight and Waist Circumference

Body weight recorded at Screening visit, Admission (Day -3) and at Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit; and waist circumference recorded at Admission (Day -3) and at Day 90 Visit, and body height recorded at the Screening visit will also be listed together with BMI (Listing 15.3.6.8). Descriptive statistics of body weight, body height, waist circumference and BMI (BMI will also be categorized as shown in Section **7.5** "**Categorical Variables**"), per timepoint will be presented (Table 15.2.6.18).

12.5.4.5.4 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -3) and at Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit will be listed by arm (Listing 15.3.6.9). Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. The number and percentage of subjects with normal, abnormal and abnormal clinically significant results will be tabulated by arm and by body systems per timepoint, including shifts in normality from Baseline (Table 15.2.6.19).

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

ECG data values and normality evaluations will be listed by arm and study day (Screening, Day -1, Day 6 and Day 90 Visit) together with changes from baseline and shift in normality. ECG data from subjects which had significant clinical findings will be flagged in listings (Listing 15.3.6.10).

Descriptive statistics will be presented for ECG data at baseline, Day 6 and Day 90 Visit by arm. ECG data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results (Table 15.2.6.20 and Table 15.2.6.21).

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 [redacted] will be responsible for the monitoring of the study. Monitoring will be performed according to [redacted] standard operating procedures (SOPs) and as per the agreed monitoring plan with PMI.

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

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

13.2 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 – Per Protocol Population
15.2.3.3.1	Descriptive Statistics of Blood COHb (%) – Per Protocol Population

TFL no.	Title
15.2.3.3.1.1	Descriptive Statistics of Blood COHb (%) by Sex – Per Protocol Population
15.2.3.3.1.2	Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – Per Protocol Population
15.2.3.3.1.3	Descriptive Statistics of Blood COHb (%) by Product Use Category – Per Protocol Population
15.2.3.4.1	Descriptive Statistics of MHBMA in Urine (units) – Per Protocol Population
15.2.3.4.1.1	Descriptive Statistics of MHBMA in Urine (units) by Sex – Per Protocol Population
15.2.3.4.1.2	Descriptive Statistics of MHBMA in Urine (units) by Cigarette Consumption – Per Protocol Population
15.2.3.4.1.3	Descriptive Statistics of MHBMA in Urine (units) by Product Use Category – Per Protocol Population
15.2.3.5.1	Descriptive Statistics of 3-HPMA in Urine (units) – Per Protocol Population
15.2.3.5.1.1	Descriptive Statistics of 3-HPMA in Urine (units) by Sex – Per Protocol Population
15.2.3.5.1.2	Descriptive Statistics of 3-HPMA in Urine (units) by Cigarette Consumption – Per Protocol Population
15.2.3.5.1.3	Descriptive Statistics of 3-HPMA in Urine (units) by Product Use Category – Per Protocol Population
15.2.3.6.1	Descriptive Statistics of S-PMA in Urine (units) – Per Protocol Population
15.2.3.6.1.1	Descriptive Statistics of S-PMA in Urine (units) by Sex – Per Protocol Population
15.2.3.6.1.2	Descriptive Statistics of S-PMA in Urine (units) by Cigarette Consumption – Per Protocol Population
15.2.3.6.1.3	Descriptive Statistics of S-PMA in Urine (units) by Product Use Category – Per Protocol Population
15.2.3.7.1	Descriptive Statistics of total NNAL in Urine (units) – Per Protocol Population
15.2.3.7.1.1	Descriptive Statistics of total NNAL in Urine (units) by Sex – Per Protocol Population
15.2.3.7.1.2	Descriptive Statistics of total NNAL in Urine (units) by Cigarette Consumption – Per Protocol Population
15.2.3.7.1.3	Descriptive Statistics of total NNAL in Urine (units) by Product Use Category – Per Protocol Population
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

TFL no.	Title
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
15.2.1.4.2.3	Summary of Demographics and Other Baseline Characteristics by Product Use Category – 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
15.2.6.3	Summary of Adverse Events by System Organ Class and Preferred Term by Product Use Safety Time Period– Safety Population
15.2.6.4	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.5	Summary of Adverse Events Leading to Study Product Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.6	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.7	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population
15.2.6.8	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.9	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
15.1.1.5	Total NNAL Urinary Concentration Adjusted for Creatinine (units) Geometric Mean and 95%

13.3 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 presented below.

13.3.1 Tables, Figures and Listings

Figures	Title
15.1.1.1	Blood COHb (%) Geometric Mean and 95% CI– Per Protocol Population
15.1.1.2	MHBMA Urinary Concentration Adjusted for Creatinine (units) Geometric Mean and 95% CI – Per Protocol Population
15.1.1.3	3-HPMA Urinary Concentration Adjusted for Creatinine (units) Geometric Mean and 95% CI– Per Protocol Population
15.1.1.4	S-PMA Urinary Concentration Adjusted for Creatinine (units) Geometric Mean and 95% CI– Per Protocol Population
15.1.1.5	Total NNAL Urinary Concentration Adjusted for Creatinine (units) Geometric Mean and 95% CI– Per Protocol Population
15.1.2.1	Urinary MHBMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.2	Urinary 3-HPMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.3	Urinary S-PMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.4	Urinary total-NNAL Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.5	Exhaled CO Mean and 95% CI– Per Protocol Population
15.1.2.6	1-OHP Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.7	Urinary 1-OHP Quantity excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.8	Total NNN Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.9	Urinary Total NNN Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.10	4-ABP Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population

Figures	Title
15.1.2.11	Urinary 4-ABP Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.12	1-NA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.13	Urinary 1-NA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.14	2-NA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.15	Urinary 2-NA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.16	o-tol Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.17	Urinary o-tol Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.18	CEMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.19	Urinary CEMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.20	HEMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.21	Urinary HEMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.22	Total 3-OH- B[a]P Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.23	Urinary Total 3-OH- B[a]P Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.24	3-HMPMA Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.25	Urinary 3-HMPMA Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.26	NEQ Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI– Per Protocol Population
15.1.2.27	Urinary NEQ Quantity Excreted Over 24 hours Geometric Mean and 95% CI– Per Protocol Population
15.1.2.28	Plasma Cotinine and Nicotine Concentrations (ng/mL) Geometric Mean and 95% CI – Per Protocol Population
15.1.2.29	Systolic Blood Pressure Mean and 95% CI – Per Protocol Population
15.1.2.30	Diastolic Blood Pressure Mean and 95% CI – Per Protocol Population
15.1.2.31	Body Weight Mean and 95% CI – Per Protocol Population
15.1.2.32	Waist Circumference Mean and 95% CI – Per Protocol Population

Figures	Title
15.1.2.33	hs-CRP Geometric Mean and 95% CI – Per Protocol Population
15.1.2.34	Blood Glucose Geometric Mean and 95% CI – Per Protocol Population
15.1.2.35	MPO Arithmetic Mean and 95% CI – Per Protocol Population
15.1.2.36	LDL Arithmetic Mean and 95% CI – Per Protocol Population
15.1.2.37	HDL Arithmetic Mean and 95% CI – Per Protocol Population
15.1.2.38	TG Geometric Mean and 95% CI – Per Protocol Population
15.1.2.39	TC Geometric Mean and 95% CI – Per Protocol Population
15.1.2.40	Fibrinogen Geometric Mean and 95% CI – Per Protocol Population
15.1.2.41	Homocysteine Geometric Mean and 95% CI – Per Protocol Population
15.1.2.42	sICAM-1 Geometric Mean and 95% CI – Per Protocol Population
15.1.2.43	WBC Arithmetic Mean and 95% CI – Per Protocol Population
15.1.2.44	Platelet Counts Geometric Mean and 95% CI – Per Protocol Population
15.1.2.45	11-DTX-B2 Urinary Concentration Adjusted for Creatinine Geometric Mean and 95% CI – Per Protocol Population
15.1.2.46	Urinary 11-DTX-B2 Quantity Excreted over 24 hours Geometric Mean and 95% CI – Per Protocol Population
15.1.2.47	8-epi-PGF2α Geometric Mean and 95% CI – Per Protocol Population
15.1.2.48	8-OHdG Geometric Mean and 95% CI – Per Protocol Population
15.1.2.49	TAC Geometic Mean and 95% CI – Per Protocol Population
15.1.3.1	Questionnaire of Smoking Urges-brief Total Score and Factor Scores Arithmetic Mean and 95% CI – Per Protocol Population
15.1.3.2	Questionnaire of Smoking Urges-brief Total Score and Factor Scores Arithmetic Least Squares Mean Differences and 95% CI – Per Protocol Population
15.1.3.3	Modified Cigarette Evaluation Questionnaire Subscales Arithmetic Mean and 95% CI– Per Protocol Population
15.1.3.4	Modified Cigarette Evaluation Questionnaire Subscales Arithmetic Least Squares Mean Differences and 95% CI – Per Protocol Population

Tables	Title
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
15.2.1.3.1	Summary of Protocol Deviations – Safety Population
15.2.1.3.2	Analysis Sets and Reasons for Exclusions – All Screened Subjects
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
15.2.1.4.2.3	Summary of Demographics and Other Baseline Characteristics by Product Use Category – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – Per Prrotocol Population
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – Per Protocol Population
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – Per Protocol Population
15.2.1.4.3.3	Summary of Demographics and Other Baseline Characteristics by Product Use Category – Per Protocol Population
15.2.1.5	Summary of Current Cigarette Brands – FAS
15.2.1.6	Summary of Medical History – Safety Population
15.2.1.7	Summary of Concomitant Diseases – Safety Population
15.2.2.1.1	Descriptive Statistics of Use of CHTP 1.2 Product and CC during Confinement – Safety Population
15.2.2.1.2	Descriptive Statistics of Use of CHTP 1.2 Product and CC during Confinement – Per Protocol Population
15.2.2.2.1	Descriptive Statistics of Use of CHTP 1.2 Product and CC during the Ambulatory Period – FAS
15.2.2.2.2	Descriptive Statistics of Use of CHTP 1.2 Product and CC during the Ambulatory Period – Per Protocol Population
15.2.2.3.1	Descriptive Statistics of Use of CHTP 1.2 Product and CC during the Ambulatory Period by Product Use Time Periods – FAS

Tables	Title
15.2.2.3.2	Descriptive Statistics of Use of CHTP 1.2 Product and CC during Confinement by Product Preference – FAS
15.2.2.3.3	Descriptive Statistics of Use of CHTP 1.2 Product and CC during the Ambulatory Period by Product Preference – FAS
15.2.3.1	Analysis of Biomarkers of Exposure for the Primary Objectives – Per Protocol Population
15.2.3.2	Analysis of Urinary Quantity Excreted of MHBMA, 3-HPMA and S-PMA over 24 hours on Day 5; and total NNAL at Day 90 Visit – Per Protocol Population
15.2.3.3.1	Descriptive Statistics of Blood COHb (%) – Per Protocol Population
15.2.3.3.2	Descriptive Statistics of Blood COHb (%) – FAS
15.2.3.3.1.1	Descriptive Statistics of Blood COHb (%) by Sex – Per Protocol Population
15.2.3.3.1.2	Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – Per Protocol Population
15.2.3.3.1.3	Descriptive Statistics of Blood COHb (%) by Product Use Category – FAS
15.2.3.4.1	Descriptive Statistics of MHBMA in Urine – Per Protocol Population
15.2.3.4.2	Descriptive Statistics of MHBMA in Urine – FAS
15.2.3.4.1.1	Descriptive Statistics of MHBMA in Urine by Sex – Per Protocol Population
15.2.3.4.1.2	Descriptive Statistics of MHBMA in Urine by Cigarette Consumption – Per Protocol Population
15.2.3.4.1.3	Descriptive Statistics of MHBMA in Urine by Product Use Category – FAS
15.2.3.5.1	Descriptive Statistics of 3-HPMA in Urine – Per Protocol Population
15.2.3.5.2	Descriptive Statistics of 3-HPMA in Urine – FAS
15.2.3.5.1.1	Descriptive Statistics of 3-HPMA in Urine by Sex – Per Protocol Population
15.2.3.5.1.2	Descriptive Statistics of 3-HPMA in Urine by Cigarette Consumption – Per Protocol Population
15.2.3.5.1.3	Descriptive Statistics of 3-HPMA in Urine by Product Use Category – FAS
15.2.3.6.1	Descriptive Statistics of S-PMA in Urine – Per Protocol Population
15.2.3.6.2	Descriptive Statistics of S-PMA in Urine – FAS
15.2.3.6.1.1	Descriptive Statistics of S-PMA in Urine by Sex – Per Protocol Population
15.2.3.6.1.2	Descriptive Statistics of S-PMA in Urine by Cigarette Consumption – Per Protocol Population

Tables	Title
15.2.3.6.1.3	Descriptive Statistics of S-PMA in Urine by Product Use Category – FAS
15.2.3.7.1	Descriptive Statistics of total NNAL in Urine – Per Protocol Population
15.2.3.7.2	Descriptive Statistics of total NNAL in Urine – FAS
15.2.3.7.1.1	Descriptive Statistics of total NNAL in Urine by Sex – Per Protocol Population
15.2.3.7.1.2	Descriptive Statistics of total NNAL in Urine by Cigarette Consumption – Per Protocol Population
15.2.3.7.1.3	Descriptive Statistics of total NNAL in Urine by Product Use Category – FAS
15.2.4.1	Analysis of Biomarkers of Exposure for the Primary and Secondary Objectives – Per Protocol Population
15.2.4.2.1	Descriptive Statistics of Exhaled CO (ppm) – Per Protocol Population
15.2.4.2.2	Descriptive Statistics of Exhaled CO (ppm) – FAS
15.2.4.3.1	Descriptive Statistics of Total 1-OHP in Urine – Per Protocol Population
15.2.4.3.2	Descriptive Statistics of Total 1-OHP in Urine – FAS
15.2.4.4.1	Descriptive Statistics of Total NNN in Urine – Per Protocol Population
15.2.4.4.2	Descriptive Statistics of Total NNN in Urine – FAS
15.2.4.5.1	Descriptive Statistics of 4-ABP in Urine – Per Protocol Population
15.2.4.5.2	Descriptive Statistics of 4-ABP in Urine – FAS
15.2.4.6.1	Descriptive Statistics of 1-NA in Urine – Per Protocol Population
15.2.4.6.2	Descriptive Statistics of 1-NA in Urine – FAS
15.2.4.7.1	Descriptive Statistics of 2-NA in Urine – Per Protocol Population
15.2.4.7.2	Descriptive Statistics of 2-NA in Urine – FAS
15.2.4.8.1	Descriptive Statistics of o-tol in Urine – Per Protocol Population
15.2.4.8.2	Descriptive Statistics of o-tol in Urine – FAS
15.2.4.9.1	Descriptive Statistics of CEMA in Urine – Per Protocol Population
15.2.4.9.2	Descriptive Statistics of CEMA in Urine – FAS
15.2.4.10.1	Descriptive Statistics of HEMA in Urine – Per Protocol Population
15.2.4.10.2	Descriptive Statistics of HEMA in Urine – FAS
15.2.4.11.1	Descriptive Statistics of Total 3-OH- B[a]P in Urine – Per Protocol Population
15.2.4.11.2	Descriptive Statistics of Total 3-OH- B[a]P in Urine – FAS
15.2.4.12.1	Descriptive Statistics of HMPMA in Urine – Per Protocol Population
15.2.4.12.2	Descriptive Statistics of HMPMA in Urine – FAS

Tables	Title
15.2.4.13.1	Descriptive Statistics of NEQ in Urine – Per Protocol Population
15.2.4.13.2	Descriptive Statistics of NEQ in Urine – FAS
15.2.4.14	Analysis of NEQ over the exposure period – Per Protocol Population
15.2.4.15	Descriptive Statistics of Plasma Cotinine and Nicotine Concentrations (ng/mL) – Per Protocol Population
15.2.4.16	Analysis of Plasma Cotinine and Nicotine Concentrations over the exposure period – Per Protocol Population
15.2.4.17	Descriptive Statistics of CYP1A2 Activity (%) – Per Protocol Population
15.2.4.18	Analysis of CYP1A2 Activity (%) – Per Protocol Population
15.2.4.19.1	Descriptive Statistics of Spirometry Results – Safety Population
15.2.4.19.2	Descriptive Statistics of Spirometry Results – Per Protocol Population
15.2.4.20.1	Spirometry Interpretation of Clinical Relevance Shift from Baseline- Safety Population
15.2.4.20.2	Spirometry Interpretation of Clinical Relevance Shift from Baseline- Per-Protocol Population
15.2.4.21	Analysis of Spirometry Results – Per Protocol Population
15.2.4.22.1	Summary of Cough Assessments Over Study by Arm – Safety Population
15.2.4.22.2	Summary of Cough Assessments Over Study by Arm – Per Protocol Population
15.2.4.23.1	Summary of Cough Assessments During the Ambulatory Period by Product Use Time Periods – Safety Population
15.2.4.23.2	Summary of Cough Assessments During the Ambulatory Period by Product Use Time Periods – Per Protocol Population
15.2.4.24.1	Summary of Cough Assessments by Arm and Study Day – Safety Population
15.2.4.24.2	Summary of Cough Assessments by Arm and Study Day – Per Protocol Population
15.2.4.25.1	Analysis of Cough during the Confinement Period – Safety Population
15.2.4.25.2	Analysis of Cough during the Confinement Period – Per Protocol Population
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15.2.4.26.2	Analysis of Cough during the Ambulatory Period – Per Protocol Population
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Listings	Title
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15.3.5.3	Listing of Intent to Use Questionnaire Results
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15.3.6.6	Listing of Prior and Concomitant Medication
15.3.6.7	Listing of Vital Signs Data and Changes from Baseline
15.3.6.8	Listing of Body Weight and Waist Circumference
15.3.6.9	Listing of Physical Examination Findings, Shift and Changes from Baseline
15.3.6.10	Listing of ECG Data and Changes from Baseline
16.1.7	Listing of Randomization Schemes and Codes

13.4 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
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15.2.3.1	Analysis of Biomarkers of Exposure for the Primary Objectives – Per Protocol Population
15.2.1.1	Summary of Subject Disposition –All Screened Subjects
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15.2.6.10	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Severity – Safety Population

14 DATA PRESENTATION

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

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16 APPENDICES

16.1 Study Assessments

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

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up r
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 p**	**30 q**	**31 q**	**60 q**	**61 q**	**90 q**	**91 q**	**91 to 119**
Informed consent for study participation and three informed consents for bio-banking	●																
Admission/Discharge		●								●						●	
Information on the risk of smoking/smoking cessation advice and debriefing	●	●								●		●		●		●	
Inclusion/exclusion criteria	●	●															
Enrolment		●															
Randomization procedures				●													
Allocation to study arms					●												
Demographics, medical history	●																

	Screening	**Confinement Period**									**Ambulatory Period**						**Safety Follow-up r**
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 p**	**30 q**	**31 q**	**60 q**	**61 q**	**90 q**	**91 q**	**91 to 119**
Concomitant diseases	●																
Socio-Economic Questionnaire								●									
Vital signs b	●	●	●	●	●	●	●	●	●	●	●		●			●	
Physical examination	●	●								●	●		●			●	
Body height and weight c	●	●								●	●		●			●	
Waist circumference		●														●	
Spirometry d	●									●						●	
Prior/concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
B/U: Hematology, clinical chemistry, safety urine analysis	●			●						●		●		●		●	
Electrocardiogram	●			●						●						●	
Chest X-ray e	●																
B: HIV, hepatitis B and C	●																
Urine cotinine screening test	●	●															

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up r
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 p**	**30 q**	**31 q**	**60 q**	**61 q**	**90 q**	**91 q**	**91 to 119**
U: Urine drug screening	●	●															
B: Serum: Pregnancy test	●																
U: Pregnancy test		●								●	●		●			●	
Alcohol urine or breath test	●	●															
FTND	●														●		
Questions about smoking habits	●	●															
Intention to quit smoking in the next 6 months using Prochaska's Questionnaire	●														●		
Identification of the current CC brand	●	●															
CHTP 1.2 demonstration	●																
CHTP 1.2 product test f		●															
Question on product Preference		●															

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up r
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 p**	**30 q**	**31 q**	**60 q**	**61 q**	**90 q**	**91 q**	**91 to 119**
Collection of CC butts for accountability		•	•	•	•	•	•	•	•	•							
Collection of used CHTP 1.2 sticks for accountability		•			•	•	•	•	•	•							
Collection of empty/partially used CHTP 1.2 packs for accountability											•		•		•		
CO breath test g		•	•	•	•	•	•	•	•		•		•		•		
B: BoExp in blood: COHb [h]			•	•	•	•	•	•	•		•		•		•		
B: BoExp to nicotine in plasma: nicotine, cotinine [h]				•	•	•	•	•	•	•	•		•		•		
U: All urinary BoExp in 24-hour urine (defined as primary and secondary endpoints, and BoExp to nicotine) (see Table A1)			•	•	•	•	•	•	•		•		•		•		
B: Serum: Clinical risk endpoints: hs-CRP, MPO, blood glucose, LDL, HDL,				•								•		•		•	

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up r
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 p**	**30 q**	**31 q**	**60 q**	**61 q**	**90 q**	**91 q**	**91 to 119**
B: Plasma: Clinical risk endpoints: fibrinogen, homocysteine				●								●		●		●	
B: Serum: Clinical risk endpoint: sICAM-1				●						●		●		●		●	
B: Clinical risk endpoint: HbA1C				●												●	
B: Serum: Clinical risk endpoints: Apo A1, and Apo B				●												●	
B: Serum: Biomarkers of oxidative stress: 4-HNE, TAC				●					●							●	
B: Plasma: Clinical risk endpoints/Biomarkers of oxidative stress: 8-epi-PGF2α, PGF2α				●					●							●	
U: Clinical risk endpoints/Biomarkers of oxidative stress in 24-hour urine: 11-DTX-B2, 8-epi-PGF2α, 8-OHdG (see Table A1)				●	●					●		●		●		●	

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up r
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 p**	**30 q**	**31 q**	**60 q**	**61 q**	**90 q**	**91 q**	**91 to 119**
Intake of a cup of coffee				●					●						●		
B: CYP1A2 activity				●					●						●		
B: CYP2A6 activity		●								●						●	
Product use diary j										●	●	●	●	●	●		
Intent to Use Questionnaire (ITUQ)			●							●						●	
QSU-brief Questionnaire k			●	●	●	●	●	●	●		●		●		●		
MCEQ (modified version) l			●	●	●	●	●	●	●		●		●		●		
Assessment of cough m			●	●	●	●	●	●	●	●		●		●		●	
AE/SAE recording	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up [r]
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 [p]**	**30 [q]**	**31 [q]**	**60 [q]**	**61 [q]**	**90 [q]**	**91 [q]**	**91 to 119**
B: Bio-banking for BoExp, clinical risk endpoints and other circulating proteins [n, o]				•						•						•	
U: Bio-banking for BoExp and clinical risk endpoints [n]					•					•						•	
B: Bio-banking for transcriptomics, lipidomics and DNA methylation sequencing [n, o]				•						•						•	

Abbreviations: 4-HNE = 4-Hydroxy-2-nonenal; 8-epi-PGF2α = 8-epi-prostaglandine F2α; 8-OHdG = 8-Hydroxy-2'-deoxyguanosine; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = Adverse event; Apo: Apolipoprotein; B = Blood sample required; BMI = Body mass index; BoExp = Biomarker(s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; CYP2A6 = Cytochrome P450 2A6; DNA = Deoxyribonucleic acid; FTND = Fagerström Test for Nicotine Dependence; HbA1c = Hemoglobin A1c; HDL = High density lipoprotein; HIV = Human immunodeficiency virus; hs-CRP = High-sensitive C-reactive protein; LDL = Low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MPO = Myeloperoxidase; PGF2α = prostaglandine F2α; QSU-brief = Questionnaire of Smoking Urges (brief version); SA = Smoking abstinence; SAE = Serious adverse event; sICAM-1 = Soluble inter-cellular adhesion molecule; TAC = Total anti-oxidant capacity; U = Urine sample required; WBC = White blood cell count; TC = Total cholesterol, TG = Triglycerides.

[b] Systolic and diastolic blood pressure, pulse rate, and respiratory rate (systolic and diastolic blood pressure will also be analyzed as risk markers on Day -1, Day 6, Visit 2, Visit 3, and Visit 4 (first day of the respective visits).

[c] Including height (only at the Screening Visit).

[d] Spirometry without bronchodilator will be performed at the Screening Visit (Visit 1) at least 1 hour after having stopped smoking and must be done prior to spirometry with bronchodilator.

Spirometry post-bronchodilator will be done at Visit 1, on Day 6 and at Visit 4. On Day 6 and Visit 4, spirometry post-bronchodilator will be performed prior to product use (CC or CHTP 1.2).

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

[f] On Day -3 (Admission), after all inclusion/exclusion criteria (see section 6.2) are checked, eligible subjects will be enrolled and then perform a product test using up to 5 CHTP 1.2. After the product test, subjects not willing and ready to use the CHTP 1.2 will be discontinued.

[g] CO breath test: During the confinement period on Days -2 to Day 5, the CO breath test will be conducted once per day, preferably in the evening around 08:00 PM ± 1.5 hour in conjunction (i.e., within 30 minutes) with COHb tests, where applicable. On Day -3 and during the ambulatory period at Visit 2, Visit 3. and Visit 4 (first day of the respective visits), the CO breath tests will be conducted once per day, irrespective of time of product use.

[h] COHb: Assessments should be done in conjunction (i.e., within 30 minutes) with CO breath tests, where applicable. COHb will be assessed on a daily basis from Day -2 to Day 5. From Day -2 to Day 5, one blood sample for the COHb assessment will be collected in the evening around 08:00 PM ± 1.5 hour. At Visit 2, Visit 3, and Visit 4 (first day of the respective visits), one blood sample for the COHb assessment will be collected during the visit, irrespective of the time of product use.

[i] Nicotine/cotinine: From Day -1 to Day 5 (both study arms): one blood sample between 08:00 PM ± 1.5 hour. On Day 6 (both study arms): one blood sampling between 06:29 AM ± 1.5 h . At Visit 2, Visit 3, and Visit 4 (first day of the respective visits) in both study arms: one blood sample to be drawn during the visit, irrespective of the time of product use.

[j] Daily during ambulatory period only (from Discharge on Day 6 to Discharge at Visit 4 . Use of any tobacco/nicotine containing products will be captured in the e-diary.

[k] QSU-brief: Daily, from Day -2 to Day 5 and at every visit during the ambulatory period, i.e., Visit 2, Visit 3 and Visit 4 (first day of the respective visits).

[l] MCEQ: Day -2 to Day 5 on a daily basis, and on Visit 2, Visit 3 and Visit 4 (first day of the respective visits) for all subjects.

[m] Cough Questionnaire to be done daily from Day -2 to Day 6 prior product use but no later than 11: 30 AM. At Visit 2 Visit 3, and Visit 4 (second day of the respective visits) no later than 11:30 AM, irrespective of product use.

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

[o] Has to be done in at least 10 hours of fasting condition.

[p] All examinations listed at the Day of Discharge (Day 6) will be conducted in subjects discontinuing the study.

[q] The first and second day of each respective visit during the exposure period in the ambulatory setting.

[r] Spontaneous reporting of new AEs/SAEs by the subject and active follow-up of ongoing AEs/SAEs by the site.

Table A1 Schedule for 24-hour Urine Collection Assessments

	Baseline Period 24-hour Urine		Confinement Exposure Period 24-hour Urine					Ambulatory Exposure Period 24-hour-Urine		
Study Day	**Day -2 (Day -2 to Day -1)**	**Day -1 (Day -1 to Day 1)**	**Day 1 (Day 1 to Day 2)**	**Day 2 (Day 2 to Day 3)**	**Day 3 (Day 3 to Day 4)**	**Day 4 (Day 4 to Day 5)**	**Day 5 (Day 5 to Day 6)**	**Visit 2 (First day to Second Day)**	**Visit 3 (First Day to Second Day)**	**Visit 4 (First Day to Second Day)**
BoExp in urine [s]	●	●	●	●	●	●	●	●	●	●
Creatinine	●	●	●	●	●	●	●	●	●	●
11-DTX-B2, 8-epi-$PGF_{2\alpha}$, 8-OHdG	●	●					●	●	●	●
Ames mutagenicity test		●					●			●
Bio-banking [t]		●					●			●

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

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

[t] Samples (5 tubes of 10 mL urine for each time point) will only be taken if additional consent for the relevant sample bio-banking is given by the subject.