PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

P2R-REXC-06-EU

Study title:	A randomized, controlled, open-label, 2-arm parallel group, single center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Carbon Heated Tobacco Product 1.0 (CHTP 1.0) compared to continuing to use conventional cigarettes during 5 days in confinement.
Short title	Reduced exposure study using CHTP 1.0 during 5 days in confinement.
EUDRACT number:	Not applicable
Product name:	Carbon Heated Tobacco Product 1.0 (CHTP 1.0)
Study number	P2R-REXC-06-EU
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	Final 4.0
Revision date:	24 June 2015
Authors:	[redacted], Clinical Scientist [redacted], Biostatistician [redacted], Medical Safety Officer

Summary of Changes

Clinical Study Protocol

P2R-REXC-06-EU

	Version	Date
Current protocol	Final Version 4.0	24 June 2015
Second updated protocol	Final Version 3.0	15 June 2015
First updated protocol	Final Version 2.0	05 June 2015
Original protocol	Final Version 1.0	13 April 2015

INTRODUCTION

The main purpose of this summary of changes is to summarize:

- the main changes between the clinical study protocol P2R-REXC-06-EU (Final Version 1.0) dated 13 April 2015 and its updated version (Final Version 2.0) dated 05 June 2015.
- the administrative changes between the first updated clinical study protocol P2R-REXC-06-EU (Final Version 2.0) dated 05 June 2015 and its following updated version (Final Version 3.0) dated 15 June 2015.
- the wording changes between the second updated clinical study protocol P2R-REXC-06-EU (Final Version 3.0) dated 15 June 2015 and its following updated version (Final Version 4.0) dated 24 June 2015.

More precise details on the protocol sections changed are provided. For identification of the changes, the previous and the amended texts are provided. The new text has been highlighted in bold (e.g. new text) and deleted text has been crossed out (e.g. deleted text).

Section		Changes
From Final 3.0 to Final 4.0		
Synopsis, 4.1	**The Admission Day; Admission Day**	***Amended text:*** "…eligible subjects will be enrolled and then perform a product test, using up to 5 sticks of CHTP 1.0." ***Old text:*** *"...eligible subjects will be enrolled and then perform a product test using 3 to 5 CHTPs 1.0."* ***Reason to change:*** Due to inconsistency of wording in several sections, the wording is adapted to the change already made in the Final 2.0.
9.2.1	**Table 7 - Time Schedule – Admission (Day -3)**	***Amended text:*** Product test for CHTP 1.0 (Use of up to 5 sticks of CHTP 1.0) ***Old text:*** *"Product test for CHTP 1.0 (Use of 3 to 5 CHTPs 1.0).* ***Reason to change:*** Due to inconsistency of wording in several sections, the wording is adapted to the change already made in the Final 2.0.
From Final 2.0 to Final 3.0		
8.3	**Reporting of Serious Adverse Events**	***Amended text:*** **Phone:** **+41** [redacted] **E-mail 1:** [redacted]@pmi.com **E-mail 2:** [redacted]**.pmi.com** **Address:** Philip Morris Products S.A. R&D Innovation Cube Quai Jeanrenaud 5 2000 Neuchâtel Switzerland ***Old text:*** ***Phone:*** ~~*+41*~~ [redacted] ***E-mail 1:*** [redacted]*@pmi.com*

		E-mail 2: [redacted] ~~*.pmi.com*~~ ***Address:*** *Philip Morris Products S.A.* *R&D Innovation Cube* *Quai Jeanrenaud 5* *2000 Neuchâtel* *Switzerland* ***Reason to change:*** The phone number and the e-mail address of the Sponsor's MSO have changed.
13.1.2	**Sponsor**	***Amended text:*** **Sponsor:** Philip Morris Products S.A. Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland Tel: +41 (58) 242 2111 Fax: +41 (58) 242 2811 [redacted] Medical Safety Officer: Phone: **+41** [redacted] E-mail: [redacted]**.pmi.com** ***Old text:*** ***Sponsor:*** *Philip Morris Products S.A.* *Quai Jeanrenaud 5,* *2000 Neuchâtel,* *Switzerland* *Tel: +41 (58) 242 2111* *Fax: +41 (58) 242 2811* [redacted] , *Phone:* ~~*Mobile :*~~ *E-mail:* [redacted] ~~*.pmi.com*~~

		[redacted] *Medical Safety Officer* |
		Reason to change: The phone number and the e-mail address of the Sponsor's MSO have changed.
From Final 1.0 to Final 2.0		
	General	The version number and the revision date were updated accordingly to the most current version and date.
	General	Replacement of the current responsible Medical Safety Officer [redacted]. The Medical Safety Officer duties have been assumed by the responsible Medical Safety Officer [redacted].
5.2	**Exclusion Criteria**	***Amended text:*** * Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-up Period plus up to 3 days. ***Old text:*** * *Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, ~~hormonal contraception containing progesterone only,~~ vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-up Period plus up to 3 days. ~~Hormonal contraception with estrogen containing products is NOT allowed in this study.~~* ***Reason to change:*** According to section *6.8 Concomitant Medication* estrogens for contraception and for hormone replacement therapy will be allowed in this study. The old text containing the deleted sentences was an error. The footnote is updated accordingly.

7.3.4	**Demonstration and CHTP 1.0 Test**	***Amended text:*** On Day -3 after enrollment, subjects will have a product test, using up to 5 sticks of CHTP 1.0. ***Old text:*** *On Day -3 after enrollment, subjects will have a product test, using 3 to 5 sticks of CHTP 1.0.* ***Reason to change:*** The minimum number of three sticks is removed as some subjects might refuse to use three sticks at minimum.
9.2.3	**Exposure Period – Table 15 Time Schedule – Day of Discharge (Day 6)**	***Amended text:*** Start of Procedure: Before Discharge ~~06:29 AM ± 1 hour.~~ Procedures: Spirometry pre- and post-bronchodilatator (recording of FEV1, FVC, FEV1/FVC). ***Old text:*** Start of Procedure: 06:29 AM ± 1 hour. Procedures: Spirometry pre- and post-bronchodilatator (recording of FEV1, FVC, FEV1/FVC). ***Reason to change:*** Due to the feasibility of the conduct, spirometry can also be performed before discharge without the defined time window of 06:30 AM ± 1 hour, as no product will be used on the Discharge Day.

SYNOPSIS

Sponsor:

Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Name of Product:

Carbon Heated Tobacco Product 1.0 (CHTP 1.0)

Study Title:

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

Study Number:

P2R-REXC-06-EU, no acronym

Study Short Title:

Reduced exposure study using CHTP 1.0 during 5 days in confinement.

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 CC to CHTP 1.0 as compared to smokers continuing to use CC.

   Endpoints (Day 5):

   - BoExp to HPHCs in urine (expressed as concentration adjusted for creatinine in 24-hour urine):
     - BoExp to 1,3-butadiene: monohydroxybutenylmercapturic acid (MHBMA).
     - BoExp to acrolein: 3-hydroxypropylmercapturic acid (3-HPMA).
     - BoExp to benzene: S-phenylmercapturic acid (S-PMA).

- BoExp to carbon monoxide (CO):
  - Carboxyhemoglobin (COHb) in blood (expressed as % of saturation of hemoglobin).

Secondary Objectives and Endpoints:

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

   Related Endpoints (Day 5):

   - BoExp to CO:
     - CO in exhaled breath (expressed as ppm).
   - BoExp to HPHCs in urine (expressed as quantity excreted and concentration adjusted to creatinine):
     - BoExp to 1,3-butadiene: MHBMA (expressed only as quantity excreted) .
     - BoExp to acrolein: 3-HPMA (expressed only as quantity excreted).
     - BoExp to benzene: S-PMA (expressed only as quantity excreted).
     - BoExp to pyrene: Total 1-hydroxypyrene (Total 1-OHP).
     - BoExp to N-nitrosonornicotine: Total N-nitrosonornicotine (Total NNN).
     - BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP).
     - BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA).
     - BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA).
     - BoExp to o-toluidine: o-toluidine (o-tol).
     - BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).
     - BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA).
     - BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene.
     - BoExp to crotonaldehyde: 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA).
     - BoExp to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butadone (NNK): Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL).
2. To describe the levels of selected BoExp over the Exposure Period in smokers switching from CC to CHTP 1.0 as compared to smokers continuing to use CC.

Related Endpoints (Day 1 to Day 5):

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

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

   Related Endpoint (Day 1 to Day 5):

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

- Nicotine and cotinine in plasma.

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

   Related Endpoint (Day 5):

   - Molar metabolic ratio of paraxanthine/caffeine (CAF) in plasma.

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

   Related Endpoint (Day 1 to Day 5):

   - Number of CHTP 1.0 and CC used each day for each subject.

6. To monitor the safety profile during the study:

   Related Endpoints:

   - Incidence of adverse events (AEs)/ serious adverse events (SAEs).
   - Incidence of CHTP 1.0 malfunctions and misuse, [redacted]
   - Respiratory symptoms: cough assessment by visual analogue scale (VAS). Likert scales, and one open question.
   - Vital signs.
   - Spirometry.
   - Electrocardiogram (ECG).
   - Clinical chemistry, hematology, and urine analysis safety panel.
   - Physical examination.
   - Concomitant medications.

Exploratory Objectives and Endpoints:

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

   Related Endpoints:

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

- Questionnaire of smoking urges (brief version): Day 1 to Day 5.
- Minnesota nicotine withdrawal scale, revised version: Day 1 to Day 5.

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

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

   Related Endpoint (Day 5):

   - NEQ and BoExp in 24-hour urine.

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

   Related Endpoints:

   - Product evaluation: modified cigarette evaluation questionnaire (MCEQ) (Day 1 to Day 5).
   - Puffing topography (Day -2, Day 1, and Day 4) and the Human Puffing Topography (HPT) questionnaire.
   - Plug and diffuser analysis: smoke nicotine in plug and diffuser (Day 4).

Study Hypothesis:

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

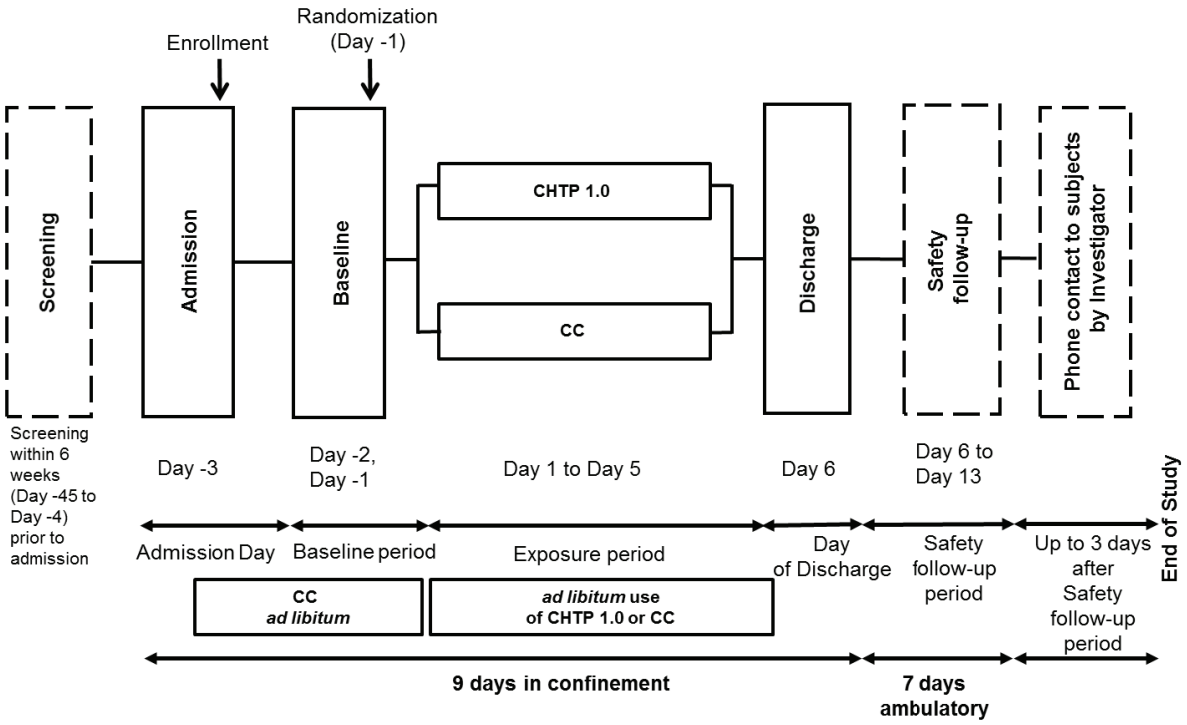
Evaluation Criterion:

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

Study Design

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

During the confinement period, adherence to product allocation (exclusive use of CHTP 1.0 in the CHTP 1.0 arm or CC in the CC arm, respectively) will be ensured by controlled distribution of each CHTP 1.0 and CC on request of the subject.



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

Figure 1 Study Design

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

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

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

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

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

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

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

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

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

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

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

  Subjects in the CC and CHTP 1.0 arms who are willing to attempt quitting during the study will be encouraged to do so and will be referred to a smoking cessation aid service. The subjects will not be discontinued from the study, will come to all scheduled visits for assessments, and his/her financial compensation will not be affected.
  Use of any tobacco/nicotine containing product other than the assigned product will not be allowed throughout the Exposure Period and may, at the discretion of the Investigator, result in the subject's discontinuation from the study.

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

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

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

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

  After Discharge, the subject will enter a 7-day Safety Follow up Period during which the follow-up of ongoing AEs/SAEs will be done by the study site. All AEs will be followed-

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

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

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

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

Study Population and Main Criteria for Inclusion/Exclusion:

Approximately 80 smoking, healthy Caucasian female or male adult subjects meeting the following main inclusion criteria:

- Subject is aged ≥ 21 years.
- Subject is Caucasian.
- Subject is healthy, as judged by the Investigator.
- Subject smokes at least 10 commercially available non-menthol CCs per day (no brand restrictions) at least for the last 6 weeks prior to admission, based on self-reporting.
- Subject has smoked at least for the last 3 years.
- Subject does not plan to quit smoking in the next 3 months.
- Subject is ready to comply with the study protocol (e.g., to use CHTP 1.0 for the duration of the study).

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

Investigational Products; Dose; and Mode of Administration:

- Carbon Heated Tobacco Product 1.0 (CHTP 1.0). CHTP 1.0 will be provided by the Sponsor.
- Subject's own preferred commercially available non-menthol single brand of CC.

Duration of Study:

The entire study duration per subject will be 17 to 61 days including a Screening Period of up to 42 days prior to Admission on Day -3, a 9-day confinement period (from Day -3 to Discharge on Day 6) followed by the 7 days for the Safety Follow-up Period (until Day 13) plus up to 3 days.

Statistical Methods:

Analysis of BoExp will be conducted on the natural log scale. The transformed Day 5 data will be analyzed by means of a generalized linear model using randomized arm as covariate adjusting for the following baseline information: sex, average cigarette consumption over the previous 4 weeks (value at admission for stratification), and baseline value of the BoExp. Estimates of differences between groups will be back-transformed to provide relative effects. Assumptions of the analysis of variance (ANOVA) model will be tested. Markedly non-log normally distributed BoExp data will be transformed or analyzed by appropriate non-parametric methods.

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

Sample Size:

A total of 80 subjects (~ 40 in the CHTP 1.0 arm, ~ 40 in the CC arm) will be randomized. This sample size is needed to attain 80% power to detect a 50% reduction or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in the CHTP 1.0 arm compared to the CC arm after 5 days of exposure, one sided test with 2.5% type I error probability.

The overall type I error will be protected by using a closed testing procedure (*i.e.*, testing the four above listed endpoints simultaneously).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADL	Activities of daily living
AE	Adverse event
ANOVA	Analysis of variance
BMI	Body mass index
BoExp	Biomarker of exposure
CAF	Caffeine
CC	Conventional cigarette(s)
CD	Compact disc
CI	Confidence interval
CHTP	Carbon Heated Tobacco Product
CO	Carbon monoxide
COHb	Carboxyhemoglobin
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 (documentation)	Curriculum vitae
CV (statistics)	Coefficient of variation
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second

FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
HPT	Human puffing topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
IxRS	Interactive web/voice response system
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MCEQ	Modified cigarette evaluation questionnaire
MedDRA	Medical dictionary for regulatory activities
MRTP	Modified risk tobacco product
PMI	Philip Morris International
PX	Paraxanthine
QC	Quality control
QSU-brief	Questionnaire of smoking urges
SA	Smoking abstinence
SAE	Serious adverse event
SAP	Statistical analysis plan
SHM	Sample handling manual
SOP	Standard operating procedure
SRO	Subject reported outcome(s)
T	Time point

T_0	Time point of first product use during study day
$t_{½}$	Half-life
[redacted]	[redacted]
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
WBC	White blood cell (count)
WHO	World Health Organization

Explanation of Terms

The following special terms are used in this protocol:

Conventional cigarette (CC)	The term 'conventional cigarette' refers to commercially available cigarettes (manufactured) and excludes cigars, pipes, bidis, and other nicotine-containing products.
Carbon Heated Tobacco Product 1.0 (CHTP 1.0)	CHTP 1.0 is a non-menthol tobacco stick which is comparable in shape and form, and is used in a similar manner to a conventional cigarette.
End of study (EOS)	The EOS for a subject is defined as Discharge on Day 6 or the date of early termination of the subject plus the 7 days for the Safety Follow-up Period plus up to 3 days to ensure that all AEs/SAEs potentially occurring during the Safety Follow-up period are fully reported. The EOS of the entire study is the end of the Safety Follow-up Period plus up to 3 days of the last subject.
Randomization	Allocation of the respective product at any time on Day -1 utilizing an interactive web and voice response system (IxRS). On Day 1, the subjects will be individually informed about the product they are randomized to prior to the first product use.
Screening failure	All subjects that are not enrolled are considered as screen failures. Re-screening of subjects who did not meet any entry criteria will not be permitted.

1 ETHICS AND REGULATIONS

1.1 Independent Ethics Committee (IEC) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF], subject information sheet, subject recruitment procedures [*e.g.*, advertisements], written information including questionnaires and instructions to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC. The IEC shall be appropriately constituted and perform its functions in accordance with the International Conference on Harmonization (ICH) Tripartite Guidance for Good Clinical Practice (GCP) [1] and local requirements, as applicable.

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

The written approval from the IEC will be filed in the Investigator file, and a copy will be filed in the study master file (SMF) at the Sponsor or designated organization. The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC.

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

These requirements for approval should in no way prevent any action from being taken by the Investigator or designee or by the Sponsor in order to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the Investigator or designee, and is implemented for safety reasons, the Sponsor and the IEC should be informed immediately.

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

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

Medically qualified study personnel will be available during the study. Separate ICFs will be signed by the subject for the collection and storage of bio-banking samples and their subsequent analysis.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [2] and is consistent with applicable regulatory principles of ICH/GCP.

The Investigator or designee agrees to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IEC. The Investigator and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki [2] is located in the Investigator's study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before or at V1, the Investigator or designee will ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the Investigator or the designee will answer all questions the subject might have to his/her full satisfaction. The subject will have sufficient time for consideration of his/her participation in the study and will be notified that he/she is free to discontinue his/her participation at any time.

Once the subject has received all the necessary information, and if he/she agrees to participate, this will be documented in the ICF by the date, time and signature of both the subject and the Investigator who conducted the inform consent discussion during Screening Visit. Any procedures specifically described in and related to the study protocol and study conduct, will not be performed before the ICF has been signed (including date and time).

The signed and personally dated original ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the subject's files and a copy must be given to the subject. The subject will be informed that if he/she discontinues from the study, the data collected until the point of discontinuation will be maintained as part of the study data and the samples collected prior to discontinuation will be analyzed, unless he/she refuses in writing.

The subject will be informed that additional data analysis not mentioned in the protocol or in the statistical analysis plan (SAP) might be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Informed Consent Form for Long-Term Bio-Banking

Separate ICFs will be signed and dated by the subject for the collection of samples and their long-term bio-banking storage. The subject's participation in the study does not depend on his/her consent to these separate ICFs.

- One separate ICF to obtain consent for serum/plasma and urine collection and long-term storage for subsequent analysis of biomarkers following completion of this study. No genetic, transcriptomics and/or lipidomics testing will be done on these samples.
- One separate ICF to obtain consent for collection and long-term storage of blood/plasma samples for further transcriptomics and lipidomics analyses.

1.3.3 Amendment to the Informed Consent Form

If a protocol amendment is required, an amendment may be required to the ICF. If a revision of the ICF is necessary, the Investigator or designee will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by the relevant IEC before subjects are informed and sign and personally date the amended ICF (including date and time).

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator and designee abide by the principles of the ICH guidelines on GCP as applicable to the study. These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting a clinical study on candidate reduced risk products. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [2].

In addition, the Investigator or designee will carry out the clinical study in accordance with applicable national and local laws of the pertinent regulatory authorities.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette smoking causes pulmonary diseases, cardiovascular diseases (CVD) and other serious diseases in smokers [3]. There is no safe cigarette, and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers cannot refrain from smoking or decide to continue smoking. For those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing products with the potential to reduce the risks of tobacco-related diseases (Reduced Risk Products [RRP]). These products are referred by the Food and Drug Administration (FDA) as modified risk tobacco products (MRTP) [4].

PMI develops candidate RRPs with the objective to substantially reduce the exposure to harmful and potentially harmful constituents (HPHCs) while providing an acceptable option to smokers as substitutes for CC. In this way, PMI can substantially reduce or eliminate a large spectrum of HPHCs. PMI's product development approaches achieve this, for example, by heating tobacco at significantly lower temperatures than CC. PMI believes that such products present the best opportunity for reducing harm because they produce vastly lower levels of HPHCs and are more likely to be accepted by smokers as substitutes for CC. Important to this effort has been the development of a product with the potential to provide nicotine in a way that closely parallels CC.

2.1.2 Description of the Product and Scientific Findings

Thousands of smoke constituents are formed when tobacco is burned or combusted. More than 6,000 of these smoke constituents have been identified [5], and more than 100 of them have been categorized as HPHCs [6].

The product developed by PMI, and to be assessed in this study, is the Carbon Heated Tobacco Product 1.0 (CHTP 1.0). With this product, the heating of the tobacco does not exceed a well-defined temperature profile, which ensures heating without combustion of the tobacco.

CHTP 1.0 is a non-menthol tobacco stick which has similar apprearance, and is used in a similar manner to a CC. To use CHTP 1.0, the consumer removes the protective cap and uses regular matches or lighter to ignite the heat source, except that this process should be done while holding CHTP 1.0 in the hand, rather than in the mouth (like for a CC). After a short pause to allow the tobacco to become heated, the aerosol generated by the heating process is inhaled by placing the filter of CHTP 1.0 in the mouth (or on the lips) and drawing air through CHTP 1.0. During use, the tobacco in CHTP 1.0 is exposed to a well-defined temperature

profile which ensures heating without combustion and at the same time provides an acceptable consumer experience in a consistent manner.

Non-clinical assessment of CHTP 1.0 showed that no new or increased toxicological hazard in the CHTP aerosol was detected compared with CC smoke. Chemical analysis of the aerosol confirmed that none of the measured HPHCs from CHTP 1.0 has increased compared to CC. The biological activity of the aerosol was tested *in vitro* and *in vivo*. A number of *in vitro* assays were performed to assess the cytotoxicity and genotoxicity of the aerosol. The subacute toxicity of the aerosol *in vivo* was evaluated in a 28-day inhalation study in rats. *In vitro* and *in vivo* results support the hypothesis that the absence of combustion when heating tobacco substantially lowers toxic effects. By heating instead of burning tobacco the aerosol of the CHTP becomes less complex, measured HPHCs are either substantially reduced or undetectable.

The non-clinical assessment of CHTP 1.0 is described in the Investigator's brochure and supports the clinical assessment of CHTP 1.0.

One clinical study (ClinicalTrials.gov Identifier: NCT00812279) has been conducted in Poland with CHTP 0.1, an earlier and non-menthol prototype version of CHTP 1.0. After 5 days of exposure marked reductions in exposure to HPHCs in the CHTP 0.1 arm and SA (smoking abstinence) arm compared to subjects continuing smoking CC were observed, and no safety concern was revealed. No clinical studies have been conducted with CHTP 1.0.

2.2 Purpose of the Study

The overall goal of the study is to demonstrate reduction in the levels of biomarkers of exposure (BoExp) to selected HPHCs and to obtain safety information in healthy subjects using CHTP 1.0 as compared to smokers continuing smoking their preferred brand of CC.

In addition, during this study data will be collected to better understand the effect of using CHTP 1.0 on excretion of mutagenic material in urine, subjective effects related to smoking, cytochrome P450 2A6 [CYP2A6] and P450 1A2 [CYP1A2] enzymatic activity and product evaluation.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Information on health risks associated with smoking and smoking cessation advice will be provided at Screening, Admission, and at Discharge. The advice will follow the recommendations of the World Health Organization (WHO) "Evidence based Recommendations on the Treatment of Tobacco Dependence"[7]. Subjects who are motivated to quit smoking during the study will be encouraged to do so, and will be referred to appropriate

medical services for necessary support and counselling. Subjects who participate in this study will also benefit from repeated and detailed health check-ups.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

- Risks related to blood sampling, e.g., excessive bleeding, fainting, hematoma, paresthesia, or infection, and the total amount of blood taken over a period of time.
- Risks related to chest X-rays, (e.g., a small increase of risk to develop cancer later in life).
- Risks related to drug applications as part of testing procedures (i.e., spirometry, and short-acting bronchodilator at the Screening Visit) per study protocol and scientifically accepted standards.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product

- Change in smoking habits due to study requirements and related concomitant symptoms (*e.g.*, craving).

All risks related to study procedures and the product will be explained in detail to the subjects.

Risk mitigation will include:

- Using commonly accepted research and scientific standards (e.g., blood samples not to exceed blood donation standards).
- Management and follow-up of adverse events (AEs)/serious adverse events (SAEs).
- Medical assessment, management of all study participants with follow-up of those who have experienced an AE(s)/SAE(s).

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detail to study participants. Unexpected malfunction of CHTP 1.0 may lead to unforeseeable risk. Subjects will be informed that CHTP 1.0 is not demonstrated to be less harmful than CC. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Primary Objective and Endpoints

The primary objective of this study is:

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

   Endpoints (Day 5):

   - BoExp to HPHCs in urine (expressed as concentration adjusted for creatinine in 24-hour urine):
     - BoExp to 1,3-butadiene: monohydroxybutenylmercapturic acid (MHBMA).
     - BoExp to acrolein: 3-hydroxypropylmercapturic acid (3-HPMA).
     - BoExp to benzene: S-phenylmercapturic acid (S-PMA).
   - BoExp to carbon monoxide (CO):
     - Carboxyhemoglobin (COHb) in blood (expressed as % of saturation of hemoglobin).

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

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

   Related Endpoints (Day 5):

   - BoExp to CO:
     - CO in exhaled breath (expressed as ppm).
   - BoExp to HPHCs in urine (expressed as quantity excreted and concentration adjusted to creatinine):
     - BoExp to 1,3-butadiene: MHBMA (expressed only as quantity excreted) .
     - BoExp to acrolein: 3-HPMA (expressed only as quantity excreted).
     - BoExp to benzene: S-PMA (expressed only as quantity excreted).
     - BoExp to pyrene: total 1-hydroxypyrene (total 1-OHP).
     - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN).

- BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP).
- BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA).
- BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA).
- BoExp to o-toluidine: o-toluidine (o-tol).
- BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).
- BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA).
- BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene.
- BoExp to crotonaldehyde: 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA).
- BoExp to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butadone (NNK): total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL).

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

   Related Endpoints (Day 1 to Day 5):

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

- HEMA.
- 3-hydroxybenzo(a)pyrene.
- 3-HMPMA.
- Total NNAL.

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

   Related Endpoint (Day 1 to Day 5):

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

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

   Related Endpoint (Day 5):

   - Molar metabolic ratio of paraxanthine/caffeine in plasma.

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

   Related Endpoint (Day 1 to Day 5):

   - Number of CHTP 1.0 and CC used each day for each subject.

6. To monitor the safety profile during the study:

   Related Endpoints:

   - Incidence of adverse events (AEs)/ serious adverse events (SAEs)
   - Incidence of CHTP 1.0 malfunctions and misuse [redacted]
   - Respiratory symptoms: cough assessment by visual analogue scale (VAS). Likert scales, and one open question.
   - Vital signs.

- Spirometry.
- Electrocardiogram (ECG).
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medications.

3.3 Exploratory Objectives and Endpoints

The exploratory objectives of this study are:

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

   Related Endpoints:

   - Excretion of mutagenic material in urine: Ames mutagenicity test (YG1024+S9) on Day 5 in 24-hour urine.
   - Subjective effects of smoking:
     - Questionnaire of smoking urges (brief version): Day 1 to Day 5.
     - Minnesota nicotine withdrawal scale, revised version: Day 1 to Day 5.
   - Cytochrome P450 2A6 (CYP2A6) enzymatic activity: the molar metabolic ratio of *trans*-3'-hydroxycotinine/cotinine: Day 6.

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

   Related Endpoint (Day 5):

   - NEQ and BoExp in 24-hour urine.

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

   Related Endpoints:

   - Product evaluation: modified cigarette evaluation questionnaire (MCEQ) (Day 1 to Day 5).
   - Puffing topography (Day -2, Day 1, and Day 4) and Human Puffing Topography (HPT) questionnaire.
   - Plug and diffuser analysis: smoke nicotine in plug and diffuser (Day 4).

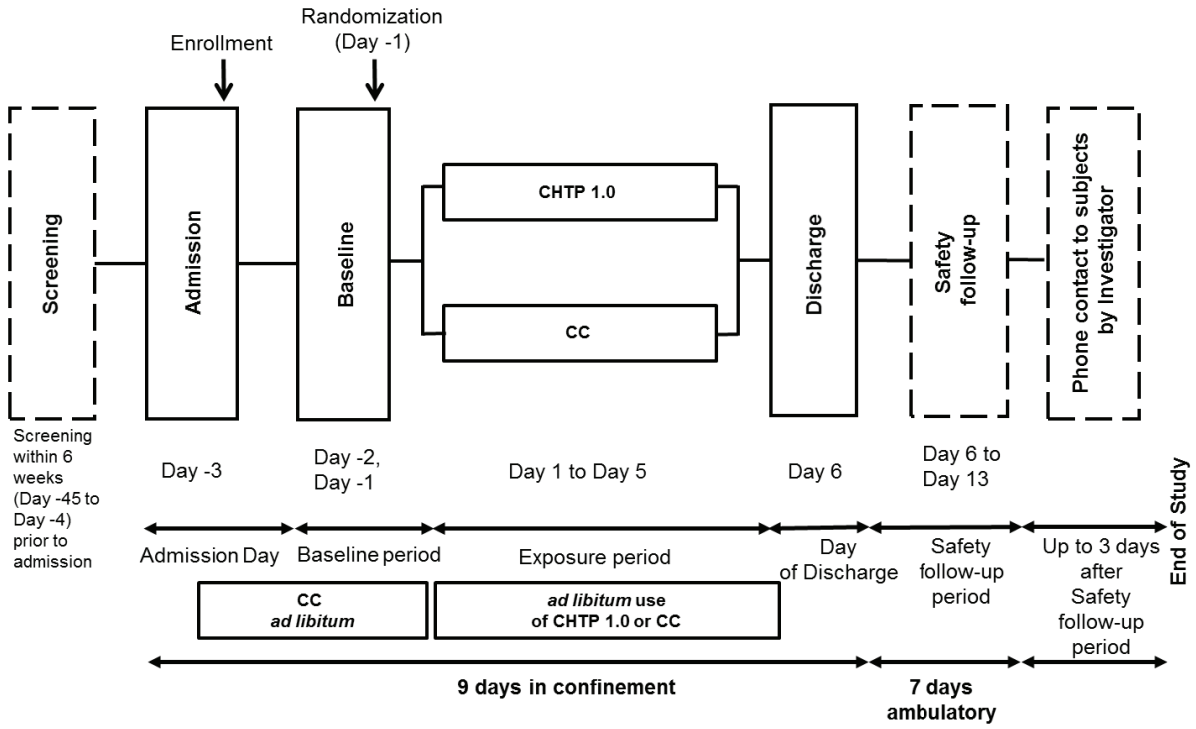
4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

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

During the confinement period, compliance to product/regimen allocation (exclusive use of CHTP 1.0 and CC in CHTP 1.0 and CC arms, respectively) will be ensured by strict distribution of each CHTP 1.0/CC on demand of the subject.



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

Figure 2 Study Design

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

  The Screening Period covers 6 weeks prior to Admission to the clinic. A demonstration of CHTP 1.0 (without product use) will be done by the site collaborators during the Screening

Visit. At Screening, spirometry needs to be done at least 1 hour after having stopped smoking. Use of any tobacco/nicotine containing product other than CC will not be allowed after the Screening Visit. Subject will be instructed not to smoke in the morning prior to the admission to the site on the Admission Day.

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

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

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

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

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

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

  Subjects will be informed of their randomized study arm by the site collaborators on Day 1 prior to 06:30 AM (the start of the Exposure Period). Subjects who do not complete the study after randomization will not be replaced.

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

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

  Subjects in the CC and CHTP 1.0 arms who are willing to attempt quitting smoking during the study will be encouraged to do so and will be referred to appropriate medical service.

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

  Twenty four-hour urine will be collected from Day 1 to Day 5 on site to measure BoExp. On Day 1, product use must not start prior to the end of urine collection of Day -1. The end

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

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

  Procedures of Discharge including but not limited to laboratory parameters will be conducted to discharge the subject from the clinic after 9 days in a confined setting. Use of CC will be allowed on Day 6 but only after 24-h urine collection is completed, and spirometry and CYP2A6 blood sampling have been performed.

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

  After Discharge, the subject will enter a 7-day Safety Follow up Period during which the follow-up of ongoing AEs/SAEs will be done by the study site. All AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the Safety Follow-up Period. Within 3 days after the end of the Safety Follow-up Period the investigator will attempt to contact the subjects by phone to check for if all AEs/SAEs potentially occurring during the Safety Follow-up Period are fully reported.

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

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

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

  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.

4.2 Rationale for Study Design

This clinical study aims to demonstrate the reduction of BoExp to selected HPHCs in smokers switching from CC to CHTP 1.0, a candidate RRP. The comparator in this study will be smokers who continue to use CC.

The Exposure Period in confinement will provide information on exposure reductions achieveable in a well-controlled environment with full control on daily CHTP 1.0 / CC consumption. The choice of HPHCs to be assessed in this study is derived from the WHO [8] and the draft guidance on "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke" [9].

In the WHO list, 9 HPHCs (acrolein, CO, 1-3 butadiene, benzene, NNN, NNK, acetaldehyde, benzo[a]pyrene, and formaldehyde) with evidence of carcinogenicity, respiratory, and cardiac toxicity were recommended to be measured as priority in the smoke chemistry for mandated lowering [8]. Exposure to 4 HPHCs (acrolein, CO, 1,3-butadiene, and benzene) among these 9 priority HPHCs will be assessed by measuring their respective BoExp as primary endpoints after 5 days of exclusive use of CHTP 1.0 and CC. The following characteristics apply to these selected BoExp:

- They are several-fold higher in smokers than in smokers abstinent from smoking [10].
- They exhibit, on average, an elimination half-life ($t_{1/2}$)of ≤ 24-hours. Therefore, the 5 days of exposure are sufficient to reach the steady state with CHTP 1.0.
- They were decreased in smokers who switched to an earlier prototype of CHTP 1.0 for 5 days, similarly to that observed in smokers who stopped smoking (data on file from a previous study with the ClinicalTrials.gov Identifier: NCT00812279).

In addition to the 9 HPHCs recommended to be measured by WHO list, the FDA has required additional 9 HPHCs for reporting to FDA (in total 18 HPHCs in cigarette smoke) [9]. From the WHO and FDA list, exposure to additional 9 HPHCs (acrylonitrile, 4-ABP, 1-NA, 2-NA, benzo[a]pyrene, crotonaldehyde, NNK, NNN, and toluene) will be assessed by measuring the respective BoExp as secondary endpoints after 5 days of exclusive use of CHTP 1.0 and CC.

Cytochrome P450 1A2 activity, which is well known to be increased by smoking and to be decreased upon smoking abstinence (SA), will be measured in this study to evaluate the effect of CHTP 1.0 use on the activity of this enzyme [11]. Cytochrome P450 2A6 activity, the enzyme involved in nicotine metabolism, will be assessed in this study to evaluate if the use of CHTP 1.0 impacts the activity of this enzyme.

Twenty-four hour-urine that will be collected in this study is the standard method to measure the levels of excretion of BoExp.

All subjects will be asked to buy their own CC according to their anticipated needs for the study in order to minimize any changes in their smoking behavior.

4.3 Appropriateness of Measurements

The BoExp measured in this study were selected based on the following criteria:

- HPHCs to be assessed in this study are derived from the list of HPHCs recommended for lowering in cigarette smoke as defined by the WHO [8] and the draft guidance on "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke" [9];
- The HPHC should be specific to the source of exposure with other sources being minor or non-existent;
- The BoExp to an HPHC should be easily detectable using reliable, reproducible, precise analytical methods;
- The HPHC should reflect a specific toxic exposure or be a reliable surrogate of exposure to HPHCs;
- The list of HPHCs should include HPHCs from both gas and particulate phase;
- The list of HPHCs should include a broad variety of chemical classes and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential) and
- BoExp represent HPHCs formed at different temperature levels.

All questionnaires utilized for this study, except the cough-VAS and HST questionnaires, are available as validated questionnaires.

4.4 Study Duration

The entire study duration per subject will be 17 to 61 days including a Screening Period of up to 42 days prior to Admission on Day -3, a 9-day confinement period (from Day -3 to Discharge on Day 6) followed by the 7 days for the Safety Follow-up Period (until Day 13) plus up to 3 days.

5 STUDY POPULATION

In total, approximately 80 smoking healthy Caucasian female or male subjects who has smoked at least 10 non-menthol CC per day for the last 6 weeks prior to Admission will be included in this study. Each sex and each of the smoking strata should have a quota applied to ensure they represent at least 40% of the study population.

The maximum number of CC is not limited. Subjects must have a smoking history of at least 3 years of smoking prior to the Screening Visit. There will be no brand restrictions. Subjects can smoke different non-menthol brands until Admission to the clinic.

From Admission to the clinic onwards, however, they must restrict themselves to one preferred, non-menthol CC brand.

5.1 Inclusion Criteria

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

Inclusion Criteria	Rationale	Screening	Admission (Day -3)
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	Administrative	X	
2. Subject is aged ≥ 21 years.	Safety	X	
3. Subject is of Caucasian origin.	Effect	X	
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).	Safety	X	X
5. Subject smokes at least 10 commercially available non-menthol CCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/CC, as labelled on the cigarette package, at least for the last 6 weeks prior to Admission, based on self-reporting.	Effect		X
6. The subject has been smoking at least for the last 3 years. The smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	
7. The subject does not plan to quit smoking in the next 3 months.	Safety	X	

Inclusion Criteria	Rationale	Screening	Admission (Day -3)
8. The subject is ready to comply with the study protocol (e.g., to use CHTP 1.0).	Effect	X	X

5.2 Exclusion Criteria

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

Exclusion Criteria	Rationale	Screening	Admission (Day -3)
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).	Safety	X	X
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).	Administrative	X	
3. Clinically relevant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric or cardiovascular disorders or any other conditions that in the opinion of the investigators would jeopardize the safety of the participant or affect the validity of the study results.	Safety	X	
4. Abnormal findings on physical examination, in the medical history, or in clinical laboratory results deemed clinically relevant by investigators (as per the common terminology criteria for adverse events [CTCAE]).	Safety	X	X
5. The subject has (FEV_1/FVC) < 0.7 and FEV_1 < 80% of the predicted value at post-bronchodilator spirometry.	Safety	X	
6. The subject has asthma condition (FEV_1/FVC < 0.75 and reversibility in FEV_1 > 12% (or > 200 mL)) from pre- to post-bronchodilator values).	Safety	X	
7. The subject has a body mass index (BMI) < 18.5 or ≥ 32 kg/m^2.	Safety	X	

Exclusion Criteria	Rationale	Screening	Admission (Day -3)
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.	Effect	X	X
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.	Effect		X
10. The subject has received medication (prescription or over-the-counter) in Table 2 (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.	Effect		X
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.	Administrative	X	X
13. The subject has a positive urine drug test.	Administrative	X	X
14. The subject has positive serology test for human immunodeficiency virus (HIV)1/2, hepatitis B or hepatitis C.	Safety	X	
15. The subject has donated or received whole blood or blood products within 3 months prior to Admission.	Safety		X
16. The subject is a current or former employee of the tobacco industry or their first-degree relatives (parent, sibling, child).	Administrative	X	
17. The subject is an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent, sibling and child).	Administrative	X	

Exclusion Criteria	Rationale	Screening	Admission (Day -3)
18. The subject has participated in a clinical study within 3 months prior to the Screening Visit.	Safety	X	
19. The subject has been previously screened in this study.	Administrative	X	
20. For women only: Subject is pregnant (does have positive pregnancy tests at the Screening and at Admission) or is breast feeding.	Safety	X	X
21. For women only: Subject does not agree to use an acceptable method of effective contraception.*	Safety	X	X

* Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-up Period plus up to 3 days. . Hysterectomy, tubal ligation, bilateral oophorectomy or post-menopausal status are reasons for not needing to use birth control. Post-menopausal status is defined as women who have not experienced menses for greater than 12 months. If a woman claims she's post-menopausal, but has had her menses within 12 months, a follicle stimulating hormone test must be performed and must be within acceptable limits.

5.3 Discontinuation of Subjects from the Study

Discontinued subjects will include both subjects who withdraw from the study (subject's decision) or subjects who are discontinued from the study by the decision of the Investigator.

Subjects will be informed that they are free to withdraw from the study (upon decision of the subject) at any time. Subjects should be questioned for the reason of withdrawal from the study, although they are not obliged to disclose it.

If the subject withdraws from the study he/she will be asked to confirm at least the following points and this information will be fully documented by Investigator or designee:

- The subject agrees to undertake the early termination procedures for safety assessments as defined in section 9.4.
- If applicable, the subject still consents for long-term biobanking (2 ICFs).
- The subject agrees that the samples collected up to the time of withdrawal will be analyzed and data collected up to the time of withdrawal will be used in the analysis and report. If the subject refuses he/she needs to document his disagreement in writing.

Subjects who terminate the study after Enrolment and prior to their individual regular discharge on the Day of Discharge (Day 6) will be asked to undertake all early termination procedures

listed in section 9.4, unless the subject refuses to perform the assessments. After the date of termination, the subject will enter into the 7-days for the Safety Follow-up Period.

Subjects who terminate the study after Enrolment and after their individual regular discharge on the Day of Discharge (Day 6), however, prior to their individual EOS and during the 7-day Safety Follow-up Period, will not be asked to undertake early termination procedures.

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

- Withdrawal of informed consent.
- Any AE or condition (including clinically significant changes in a laboratory parameter) which at the discretion of the Investigator no longer justifies the subject's participation in this study.
- Positive pregnancy testing (section 8.5).
- The Sponsor or Investigator terminates the study or the study terminates at a particular site. If the Sponsor or the Investigator decides to prematurely terminate the study, the subject will be promptly informed. The Investigator or designee should report the fact and the reason in writing to the IEC.
- Discontinuation is considered to be in the best interest of the subject or the other subjects as judged by the Investigator.
- Subjects using any nicotine/tobacco product different from the assigned product.

Subjects may be discontinued from the study for the following reason:

- Non-compliance to the study procedures based on the judgment of the Investigator.

Until randomization, subjects can be replaced, however subjects that discontinue the study after randomization will not be replaced and will not be allowed to re-enter the study.

5.4 Lost to Follow-up

Reasonable number of attempts to contact the subject (including written correspondence and phone calls) should be done and documented in the source documents by the site. The date of the last contact (e.g., last visit, last phone call) should also be recorded in the source document and corresponds to the date of the end of study of the subject. When the PI(s) or designee(s) declare(s) a subject is lost to follow-up, the lost to follow-up date will be recorded.

If the site has lost track of the subject but the subject has reached the maximum number of study days (Day 13), then the PI(s) or designee(s) will declare the subject lost to follow-up at this date.

5.5 Violation of Selection Criteria

Any subjects who do not meet the entry criteria after signing the ICF and prior to Enrolment at Day -3 will be considered as screen failures and will be replaced by other subjects. Re-screening of subjects will not be permitted.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

- CHTP 1.0

CHTP 1.0 is a non-menthol tobacco stick which is comparable in shape and form, and is used in a similar manner to CC. To use CHTP 1.0, the consumer removes the protective cap and uses a conventional lighting method to ignite the heat source. After a short pause to allow the tobacco to become heated, the aerosol is generated by drawing air through CHTP 1.0. During use, the tobacco in CHTP 1.0 is heated and does not exceed a well-defined temperature profile which ensures heating without combustion of the tobacco and at the same time provides an acceptable consumer experience in a consistent manner.

CHTP 1.0 will be provided by the Sponsor and its distribution will be limited to an appropriately trained study site collaborator. Additional information are provided in section 2.1.2.

The overall objective of CHTP 1.0 is to provide an acceptable experience in which the HPHC level in the aerosol is substantially reduced in comparison with CCs.

- CC

Commercially available non-menthol CC (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/CC, as labelled on the cigarette package, will be used as a reference product to CHTP 1.0. CC will not be provided by the Sponsor.

All eligible subjects will be asked to purchase their own preferred single-brand of non-menthol CC prior to Admission. As randomization takes place at any time on Day -1, every study subject needs to buy his/her anticipated amount of single-brand CC for a total of 9 days plus 2 extra packs.

6.2 Packaging and Labeling

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

Each pack of CC provided by the subject will be labeled to identify which subject the CCs belong to (labels should be affixed to the cellophane of the lower part of the pack).

For CHTP 1.0, the packs will be labelled with the necessary information including, but not limited to, product code and expiry date.

6.3 Use of Investigational Product(s)

Subjects will never be requested or forced to smoke or to use the CHTP 1.0 and will be free to stop smoking at any time during the study. The study is designed as an *ad libitum* use study.

During the Screening Period, subjects will be allowed to smoke according to their smoking habits except during the procedures of the Screening Visit (section 9.1) Subject will be instructed not to smoke in the morning prior to Admission on Day -3.

6.3.1 Admission Day (Day -3 to Day -2)

Smoking *ad libitum* will be allowed throughout the day. All subjects will be allowed to continue smoking *ad libitum* their single preferred brand of usual CC.

After Enrolment, all subjects will undergo a CHTP 1.0 product test. If subject is not willing to use CHTP 1.0 after the product test, he/she will be discontinued from Enrolment and undergo early termination procedures, followed by a 7-day Safety Follow-up Period.

6.3.2 Baseline Period (Day -2 to Day 1)

During the Baseline Period, all subjects will be allowed to continue smoking *ad libitum* their single preferred brand of non-menthol CC.

6.3.3 Exposure Period (Day 1 to Day 5)

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

- CHTP 1.0 arm

Subjects randomized to the CHTP 1.0 arm will use exclusively CHTP 1.0 from Day 1, 06:30 AM onwards until Day 5, 11:00 PM.

- CC arm

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

6.3.4 Day of Discharge (Day 6)

Use of CC will be allowed on Day 6 but only after twenty four-hour urine collection of Day 5 is completed, and spirometry and CYP2A6 blood sampling have been performed.

6.3.5 Safety Follow-up Period

During the Safety Follow-up Period (after discharge at Day 6 until Day 13), all subjects are free to smoke their own CC *ad libitum*.

6.3.6 Stopping Rules for Investigational Product

For safety purposes, smoking should be temporarily stopped in the event of any signs suggesting nicotine overexposure, (e.g., gastrointestinal disturbance [nausea, vomiting, diarrhea, stomach or abdominal pain], cold sweats, headache, dizziness, and breathing problems) or any reasons at the discretion of the Investigator or designee.

6.4 Method for Assigning Subjects to Study Arms

When all the eligibility criteria have been met, randomization will be done through the interactive web and voice response system (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 1.0:CC in a 1:1 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 (smokers smoking 10 to 19 CC/day and smokers smoking > 19 CC/day). In each arm, each sex and each of the smoking strata should have a quota applied to ensure they represent at least 40% of the population.

6.5 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 Description of Blinded Study Personnel

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[b].
PMI Clinical Scientist	After the finalization of PMI blind database review[b]. Can be actively un-blinded when appropriate.

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

[b] 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.

6.6 Investigational Product Accountability and Compliance

6.6.1 Dispensing Investigational Product

From Day -3 onwards to Day 5, the Investigational Product (IP) CC, and from Day 1 onwards to Day 5, the IP CHTP, will be dispensed to the subjects stick by stick. One will be allowed at a time and documented in an appropriate log.

On each day of the confinement period, the time of dispense and return for each product (CC/CHTP 1.0) use has to be documented from Day -3 for CC and from Day 1 for CHTP 1.0 onwards.

CHTP 1.0 will not be promoted for commercial distribution or test market.

6.6.2 Storage and Accountability

CHTP 1.0 and CC will be stored in a secured storage site with access limited to authorized personnel only. The study collaborator designated by the Principal Investigator will be responsible for the storage and accountability of the IPs in accordance to sponsor's requirements. CHTP 1.0 must be stored under controlled conditions (temperature and humidity), whereas CCs can be stored in normal conditions (at ambient temperature with no temperature or humidity control).

Subjects will return each used CHTPs 1.0 or butt of each used CC immediately after use to the site collaborators for accountability. The time of return of the products will be documented in an appropriate log. At the end of the study, unused CCs given to the site collaborators at Admission will be given back to the subjects.

6.6.3 Investigational Product Retention

Used and unused CHTP 1.0 will be destroyed or returned to the Sponsor upon study completion as per instructions which will be provided by the Sponsor in due time.

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

6.6.4 Compliance to Investigational and Reference Products

Compliance for all study arms will be ensured by strict distribution of the products (stick by stick) and collection of the CC butts and CHTP 1.0 after each use. Distribution and return of these products will be documented in appropriate logs.

6.7 Restrictions

6.7.1 Smoking Restrictions

At the Screening Visit pre- and post-bronchodilator spirometry will be done at least 1 hour after having stopped smoking. Subjects will be instructed not to smoke in the morning of Day -1 and the Day of Discharge (Day 6) until twenty four-hour urine collection of Day 5 is completed, blood drawing for CYP2A6 activity assessment and spirometry will have been performed.

During the confinement period, smoking will generally only be allowed during the designated smoking times, from 06:30 AM to 11:00 PM.

Subjects will not have free access to their CC or CHTP 1.0 which will be dispensed by the site collaborators individually as described in section 6.6.1.

To avoid cross smoke contamination between the two study arms, subjects must use their assigned product (CHTP 1.0 or CC) in separate smoking rooms.

Using CHTP 1.0 or smoking CC will not be allowed during study procedures.

6.7.2 Dietary Restrictions

A standard diet will be designed by a dietician for the whole confinement period. For each meal, the caloric and fat content should be controlled in order to avoid a “high-fat” diet. A “high-fat” diet is defined as a diet which contains “approximately 50 percent of total caloric content of the meal [from fat] and is high in calories (approximately 800 to 1000 calories)” [12].

In order to avoid any effect on assessment of biomarkers of exposure, grilled or pan-fried meat, pre-cooked meats (e.g. tuna, ham, corned beef, and smoked meats), bacon and sausage will not be permitted. In addition, alcohol, broccoli, brussels sprouts, cauliflower, grapefruit and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana, etc.) will not be allowed except when you are asked to drink a cup of coffee for one of the assessment (you will be instructed accordingly by your site staff).

Subjects are not allowed to bring their own food (including sweets or chewing gum, etc.) or beverages to the investigational site. Meals will be served according to the agreed schedules. Additional light snacks, fruits (with the exception of grapefruits), and raw vegetables can be distributed to the subjects without restrictions at any time during confinement as long as they comply with the dietician’s standard diet. Consumption of non-carbonated water is allowed, however, should be carefully monitored. Consumption of quinine-containing drinks (*e.g.*, tonic water) is not allowed during the study. The same menu and meal schedule will be administered uniformly for all subjects in all study arms.

In addition, for the purpose of the Ames test planned on Day -1 and Day 5, the menus served on Day -2 and Day 4 will be identical.

Fasting state has to be observed for at least 10 hours prior to blood drawings for the safety laboratory on Day -1, on Day 6, for blood/plasma samples for further transcriptomics and lipidomics analyses on Day -1 and Day 6.

6.8 Concomitant Medication

For the purpose of this study, no concomitant medication should be taken by the subjects from Screening to Discharge without prior informing the Investigator or designee. Any medication with an impact on the CYP1A2 and CYP2A6 metabolism (as prescription and over-the-counter products) as presented below in Table 2 must be avoided.

Prior to database lock, concomitant medication will be assessed according to their potential impact on CYP1A2 and CYP2A6 activity and potential impact on the study results.

Concomitant medication and prior medications will first be assessed at Screening Visit. To be eligible for the study, any medication with impact on CYP1A2 and CYP2A6 metabolism must be discontinued at least 14 days or for at least 5 half-lives (whichever is longer) prior to admission to the site. They must not be used during the entire study until Discharge. It is at the discretion of the Investigator or designee to assess if the termination of such medication at Screening is medically justified and safe for the subject.

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

The following drugs and substances are examples considered as having an impact on CYP1A2 and CYP2A6 activity (Table 2). Prior to database lock, the concomitant medication will be assessed according to the potential impact on CYP1A2 and CYP2A6 activity and the potential impact on study results.

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

CYP1A2 Inhibitors [13]	Pharmacologic Category
Amlodipine	Antihypertensive; calcium channel blocker
Cimetidine	Histamine H2 antagonist
Ciprofloxacin	Antibiotic, fluoroquinolone

Fluvoxamine	Antidepressant, selective serotonin reuptake inhibitor
Fospropofol	General anesthetic
Gemfibrozil	Antilipemic agent, fibric acid
Ketoconazole	Antifungal agent, topical
Diclofenac	NSAID
Methoxsalen	Psoralen
Mexiletine	Antiarrhythmic agent
Miconazole	Antifungal agent, topical

CYP1A2 Inhibitors [13]	Pharmacologic Category
Nifedipine	Antihypertensive, calcium channel blocker
Norfloxacin	Antibiotic, fluoroquinolone
Propofol	Systemic general anesthetic
Primaquine	Aminoquinoline (antimalarial)
Ofloxacin	Antibiotic, fluoroquinolone
Thiabendazole	Antihelmintic agent
Tranylcypromine	Antidepressant, monoamine oxidase inhibitor
Zileuton	5-lipoxygenase inhibitor

CYP1A2 Inducers [13]	Drug Class
Carbamazepine	Anticonvulsant
Phenobarbital	Anticonvulsant, barbiturate
Primidone	Anticonvulsant, barbiturate
Rifampin	Antibiotic, antitubercular agent

CYP1A2 Substrates [13]	Drug Class
Acenocoumarol	Anticoagulant
Alosetron	Antiemetic, selective 5-HT3 receptor antagonist
Aminophylline	Phosphodiesterase enzyme inhibitor, nonselective
Betaxolol	Antihypertensive, beta-blocker
Caffeine	Central nervous system stimulant, phosphodiesterase enzyme inhibitor
Clomipramine	Antidepressant, tricyclic
Clozapine	Antipsychotic agent
Cyclobenzaprine	Skeletal muscle relaxant
Dacarbazine	Antineoplastic agent, alkylating agent

Duloxetine	Antidepressant, serotonin/norepinephrine reuptake inhibitor
Estradiol	Estrogen derivate
Estrogens, conjugated A/synthetic	Estrogen derivate
Estrogen, conjugated equine	Estrogen derivate
Estrogen, esterified	Estrogen derivate
Estropipate	Estrogen derivate
Flutamide	Antineoplastic agent, antiandrogen
Fluvoxamine	Antidepressant, selective serotonin reuptake inhibitor

CYP1A2 Substrates [13]	Drug Class
Guanabenz	Antihypertensive, central Alpha-2 adrenergic agonist
Mexiletine	Antiarrhythmic agent, class Ib
Mirtazapine	Antidepressant, alpha-2 antagonist
Olanzapine	Antimanic agent, antipsychotic agent
Pimozide	Antipsychotic agent
Propranolol	Antihypertensive, beta-blocker
Ramelteon	Hypnotic
Rasagiline	Anti-Parkinson's agent, MAO type B inhibitor
Riluzole	Glutamate inhibitor
Ropinirole	Anti-Parkinson's agent, dopamine agonist
Ropivacaine	Local anaesthetic
Tacrine	Anti-Alzheimer agent, cholinesterase inhibitor
Theophylline	Phosphodiesterase enzyme inhibitor, nonselective
Thiothixene	Antipsychotic agent
Tizanidine	Alpha-2 adrenergic agonist
Trifluoperazine	Antipsychotic agent

CYP2A6 Inhibitors [13]	Drug Class
Amiodarone	Antiarrhythmic agent, class III
Desipramine	Antidepressant, tricyclic
Isoniazid	Antitubercular agent
Ketoconazole	Antifungal agent, topical
Letrozole	Antineoplastic agent, aromatase inhibitor
Methoxsalen	Psoralen

Miconazole	Antifungal agent, topical
Tranylcypromine	Antidepressant, monoamine oxidase inhibitor

CYP2A6 Inducers [13]	Drug Class
Amobarbital	Barbiturate
Pentobarbital	Anticonvulsant, barbiturate
Phenobarbital	Anticonvulsant, barbiturate
Rifampin	Antibiotic, antitubercular agent
Secobarbital	Barbiturate

CYP2A6 Substrates [13]	Drug Class
Dexmedetomidine	Alpha-2 adrenergic agonist, sedative
Ifosfamide	Antineoplastic agent, alkylating agent

The Investigator is responsible for the medical care of the subjects during their participation in this study.

If the use of a concomitant medication cannot be avoided for the subject's safety, it has to be fully documented (section 7.3.5). Concomitant medications should be followed up with the CRO Medical Monitor on an ongoing basis.

7 STUDY PROCEDURES

Personnel performing or recording study assessments must have appropriate and fully documented training. Quality control (QC) measures have to be in place. An overview of all study assessments is shown in the schedule of events (Appendix A). Considering that not all subjects can have a procedure at the same time point, adequate time windows will be given for each study procedure and each time point in section 9. Site personnel will adhere to the site's standard operating procedures (SOPs) for all activities or otherwise specified by the protocol. Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

7.1 Informed Consent

Prior any study assessments is performed, the subject will be asked to provide his/her written consent to participate to the study (ICF) (section 1.3). All assessments must start after the time of ICF signature by the subject for study participation.

In addition to the ICF for study participation, the subject will be asked to provide his/her separate consent for sample bio-banking (section 1.3.2).

The subject's participation in the study does not depend on his/her consent for sample bio-banking and will be separated from the consent for study participation. The different consents will be captured in the CRF.

7.2 Smoking Cessation Advice and Debriefing

Each subject will be given advice on the risks of smoking, with smoking cessation (SC) advice, three times during the study: at the Screening Visit, at Admission on Day -3, and at Discharge on Day 6. The form of a brief interview will be used according to current WHO recommendations [7]. Details of the interview will be recorded in the source document file. Information on the risk of smoking/smoking cessation advice will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the Investigator and may additionally be given in a group session.

In addition to the information of the risk of smoking/SC advice, a debriefing of subjects will be done together with information on the risk of smoking and SC advice to address any intended or unintended beliefs participants have about CHTP 1.0. The goal of the debriefing is to ensure that subjects exit the study with an accurate understanding of product risks including an understanding that CHTP 1.0 has not been demonstrated to be less harmful than CC.

7.3 Clinical Assessments

The results of the clinical assessments described in this section will be recorded in the CRF.

7.3.1 Demographic Data

Demographic data (gender, age, race and/or ethnicity) will be recorded.

See Appendix A for the timepoints of assessment.

7.3.2 Identification of the Current Cigarette Brand

Identification of the current non-menthol CC brand smoked by the subject will be done at the Screening Visit and at Admission. Subjects will be asked to bring their own supply of current CC brand to the site and will have to hand their CC supply for the confinement period to the site collaborators. The site staff will document the brand name and yields in the source documentation.

7.3.3 Questions on Smoking History/Habits and Intention to Quit Smoking.

Subjects will be asked by the site collaborators the following questions about their smoking history and habits:

1. Have you smoked for at least the past 3 years? (yes/no)
2. How many years have you smoked? (numeric response, 2 digits)
3. On average, how many cigarettes per day have you smoked over the last 6 weeks? (numeric response, 2 digits)
4. On average, how many cigarettes per day have you smoked since you started smoking? (numeric response, 2 digits)
5. Have you used nicotine-containing products other than commercially available non-menthol CC within 6 weeks prior to admission? For example, any tobacco-based products or NRT, electronic cigarettes, or similar devices. (NOTE: This question is to be asked on the Admission Day only.)
6. On average, how would you describe your e-cigarette use over the last year? (check one)
    a. Daily.
        i. How much use per day? (numeric response, 2 digits)
    b. Weekly.
        i. How much use per week? (numeric response, 2 digits)
    c. Sporadically. (less than once per week)
    d. Tried e-cigarettes. (between 1 – 10 uses)
    e. Never tried e-cigarettes.

7. Are you planning to quit smoking during the next 3 months? (yes/no)

This self-reported CC daily consumption will be used to assess eligibility at the Screening Visit or on the Admission Day.

See Appendix A for the timepoints of assessment.

7.3.4 Demonstration and CHTP 1.0 Test

All subjects will have a demonstration of CHTP 1.0 at the Screening Visit. On Day -3 after enrollment, subjects will have a product test, using up to 5 sticks of CHTP 1.0. Only subjects willing and ready to use CHTP 1.0 will continue in the study.

7.3.5 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical history and any concomitant disease will be documented at the Screening Visit. Medical history is defined as any condition that started and ended prior to the Screening Visit. A concomitant disease is defined as any condition that started after ICF signature or was started prior to the Screening Visit and is still ongoing at the Screening Visit.

Prior medication taken within 4 weeks prior to Screening Visit and any concomitant medication needs to be documented. Any medication which was started prior to the Screening Visit and is still being taken by the subject will be considered as concomitant medication. Medication initiated after Screening is also referred to as concomitant medication. This applies to both prescription and over-the-counter products.

Records should include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), total daily dose/unit (expressed in metric units, for example, mg, mL, or IU), indication, and the start and, if applicable, the stop date (day, month, and year). Therapy changes (including changes of regimen) during the study have to be documented. If a concomitant medication is still being taken by the subject at the end of the study, this will be recorded in the CRF.

7.3.6 Physical Examination

A physical examination will be conducted at the Screening Visit, at Admission and at Discharge.

See Appendix A for the timepoints of assessment.

7.3.7 Body Height and Weight

Body weight will be recorded at the Screening Visit, at Admission and at Discharge. Body height will be measured at the Screening Visit only. The BMI will be calculated from the body weight and height using the following formula:

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

See Appendix A for the timepoints of assessment.

7.3.8 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate will be measured in the morning at applicable visits. All measurements will be made after the subject has rested for at least 5 minutes in a supine position.

For every measurement of vital signs, it has to be ensured and documented that the duration between the end of last smoking and the measurement should be at least 15 minutes.

See Appendix A for the timepoints of assessment.

7.3.9 Other Clinical Assessments

7.3.9.1 Spirometry

All personnel performing lung function testing must have the appropriate training according to local requirements with the record of the training. Quality control measures should be available and be properly documented. In a sitting position, the subject will be at rest for at least 15 minutes prior to lung function testing, i.e. pre and post-bronchodilator application. All lung function maneuvers will be recorded with the subject in a sitting position throughout the study.

The spirometry test will be performed in accordance with the 2005 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry [14].

The spirometry tests will include the recording of FEV_1, FVC and FEV_1/FVC ratio.

All spirometry testing must be performed at least 1 hour after having stopped smoking (if applicable).

See section 6.7.1 for the smoking restrictions associated spirometry.

Pre and post- bronchodilator spirometry tests will be performed. The ratio of FEV_1/FVC will be calculated from the highest acceptable FEV_1 and the highest acceptable FVC, respectively. All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of around 400 µg of salbutamol/albuterol (usually equivalent to 4 puffs assuming 100 µg/puff). The time of salbutamol/albuterol inhalation and time of spirometry assessment will be recorded in the source document.

The results from FEV_1 and the ratio FEV_1 to FVC at the Screening Visit will be used for eligibility criteria to assess spirometry and asthma conditions.

For all the other visits, pre- bronchodilator spirometry will be used to describe the changes in pre-spirometry measurements over the duration of the study. Values for FEV_1 and FVC will be recorded. The ratio FEV_1/FVC will be calculated from the highest acceptable FEV_1 and the highest acceptable FVC respectively.

See Appendix A for the timepoints of assessment.

7.3.9.2 Electrocardiogram

Electrocardiogram (ECG) recording will be performed as per the site's local practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QT interval corrected by the ECG machine according to Bazett's formula and Federici's formula. Every ECG has to be assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis has to be provided on the eCRF for all ECGs assessed as abnormal – clinically relevant. All ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents and signed by Principal Investigator or designee.

See Appendix A for the timepoints of assessment.

7.3.9.3 Chest X-ray

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

7.4 Biomarker Assessment

All bioanalytical assays and laboratory assessments (section 7.5) will be carried out using validated methods. The bioanalytical methods used will be documented in the bioanalytical reports. A list of laboratories is provided in Appendix B.

Precautions should be taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine or CO.

7.4.1 Biomarker of Exposure

7.4.1.1 Biomarker of Exposure to CO and COHb

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

- CO breath test:

  CO in exhaled breath will be measured using the Smokerlyzer® (*e.g.*, Micro 4 Smokerlyzer® device or similar).

  A CO breath test will be conducted once per day, preferably in the evening around 8:00 PM. The CO breath test should be conducted in timely conjunction with the blood sampling for COHb.

  See Appendix A for the timepoints of assessment.

- COHb test:

  Tests for COHb measurement will be performed at a designated laboratory. One blood sample will be taken in the evening around 8:00 PM. The COHb sampling should be conducted in timely conjunction with the CO breath test.

  See Appendix A for the timepoints of assessment.

7.4.1.2 Plasma Nicotine and Cotinine

Nicotine and cotinine concentrations will be measured in plasma to evaluate the exposure to nicotine.

One blood sample in subjects in the CHTP 1.0 and CC arm will be taken in the evening around 8:00 PM.

See Appendix A for the timepoints of assessment.

7.4.1.3 Biomarkers of Exposure to HPHCs

The following BoExp to HPHCs will be measured in 24-hour urine collection samples as per the schedule of events (Appendix A):

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

BoExp to HPHCs in urine will be expressed as quantity excreted, and their concentrations will be adjusted to creatinine. For normalization of BoExp to HPHCs, creatinine will also be measured in the 24-hour urine samples.

7.4.2 CYP1A2 Activity Test

CYP1A2 activity will be assessed in plasma by measuring paraxanthine (PX) and caffeine (CAF) concentrations and calculating the PX/CAF molar metabolic ratio. Samples to measure PX and CAF will be drawn approximately 6 hours (±15 minutes) after the intake of a cup of coffee made from 4.2 g (±10%) regular instant coffee (Nescafé Gold Instant; Nestlé; Deutschland; CAF content: 72 mg/2 g) with 150 ml ±10 ml water. The CAF content will be approximately 150 mg CAF (11).

The exact time of intake of the cup of coffee in the morning and of the time of blood sampling 6 hours [±15 minutes] later must be recorded.

See Appendix A for the timepoints of assessment.

7.4.3 CYP2A6 Activity Test

CYP2A6 activity will be measured in plasma using the molar metabolic ratio of *trans*-3'-hydroxycotinine to cotinine. CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites. CYP2A6 blood sampling has to be done prior to smoking.

See Appendix A for the timepoints of assessment.

7.4.4 Ames Mutagenicity Test

Urine mutagenicity, a biomarker for measuring mutagen load, will be measured in 24-hour urine.

The urinary determination of each sample will be done in one bacterial strain (S. typhimurium strain YG1024) using S9 metabolic activation and 4 doses for each of the urine extracts.

See Appendix A 1 for the timepoints of assessment.

7.5 Laboratory Assessments

A list of laboratories is provided in Appendix B.

7.5.1 Clinical Chemistry, Hematology, and Urine Analysis for Safety Panel

Hematology, clinical chemistry, and urine analysis for the safety panel will be measured at Screening, on Day -1 and at Discharge on Day 6 (Day of Discharge). Tests will be conducted at a local laboratory or the site. Blood will be taken after no less than the 10 hours of fasting

except at the Screening Visit (section 6.7.2). The urine test/urine analysis safety panel will be performed at a local laboratory. Parameters to be measured are listed in Table 3.

Table 3 Hematology and Clinical Chemistry Parameters (Safety)

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

See Appendix A for the timepoints of assessment.

7.5.2 Serology

A test for hepatitis B surface antigen, hepatitis C virus and human immunodeficiency virus (anti-HIV1/2 and p24 antigen) will be done. In case of positive results, the subject will be referred to appropriate medical care.

See Appendix A for the timepoints of assessment.

7.5.3 Urine Drug Screening

The urine will be screened for the following drugs or class or drugs: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates.

See Appendix A for the timepoints of assessment.

7.5.4 Urine Cotinine Screening

A urine dip-stick or casette cotinine test will be performed to confirm the subject's smoking status. The test must detect cotinine with a cotinine threshold of ≥ 200 ng/mL, (*e.g.*, One-Step Cotinine Test 008A086, Ultimed, Belgium).

See Appendix A for the timepoints of assessment.

7.5.5 Alcohol Breath Test

Subjects will undertake a breath alcohol test using an alcometer device (*e.g.*, Alcotest 7410 Plus, Dräger).

See Appendix A for the timepoints of assessment.

7.5.6 Urine Pregnancy Test

All female subjects will have pregnancy testing at the Screening Visit, at Admission to the clinic and at Discharge. Female subjects with a positive pregnancy test at the Screening Visit or at Admission will not be enrolled and will be considered as screen failures. In case of any positive urine pregnancy test, the Investigator or designee will inform the subject about the risks associated with smoking during pregnancy.

The post-menopause is formally defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation) without a period. If a woman claims she is post-menopausal, but has had her menses within 12 months, a follicle stimulating hormone test must be performed and must be within acceptable limits of the post-menopausal status. When the post-menopausal status of a female is confirmed, the pregnancy test scheduled during the study will not be done.

In the event of an unclear urine pregnancy test, absence of pregnancy should be confirmed by a serum follicle stimulating hormone level >20 IU/l.

All pregnancies detected during the study must be reported and handled as described in section 8.5.

See Appendix A for the timepoints of assessment.

7.6 Sample Handling, Storage, and Shipment

All blood samples are to be tested at a central laboratory with the exception of the safety laboratory panel which will be tested at a local laboratory (see Appendix B). The urine dip-stick for the safety laboratory, urine pregnancy tests, urine drug screening, and urine cotinine tests will be done by personnel at the study sites.

Detailed procedures for collection and handling of samples are described in a separate sample handling manual (SHM). Safety laboratory samples will be destroyed as per the laboratory's standard procedures. All primary and back-up samples for the assessments of BoExp (except bio-banking samples) of discontinued subjects will be destroyed after the bioanalytical report has been finalized or the database has been locked, whichever comes last. Personnel at the facility/-ies where samples are stored will be informed in writing by the Sponsor when destruction of the samples will be allowed.

The bioanalytical lab(s) will be listed in the SHM.

7.6.1 Blood Samples

Blood samples will be collected by qualified and trained site personnel. Subjects should be in a seated position during blood collection. The maximal total volume of blood drawn for each subject will be around 180 mL, which includes about 20 mL for safety and repeated analysis, about 20 mL for long-term storage of the bio-banking samples for further analysis of biomarkers (only if additional consent is given) and 20 mL for long-term storage bio-banking samples for further analysis of transcriptomics and lipidomics (only if additional consent is given) (section 7.6.3).

The blood sampling for transcriptomics and lipidomics, and the data related to these samples will be anonymized. Anonymized data and samples are initially single or double coded where the link between the subjects' identifiers and the unique code(s) is subsequently deleted.

7.6.2 Urine Samples

Spot urine samples will be used for the urine drug screening, urine cotinine test, urine pregnancy test and safety urine analysis.

Twenty four-hour urine will be collected from Day -2 to Day 6 on site to measure BoExp. On Day 1, product use must not start prior to the end of urine collection of Day -1.

Twenty four-hour urine sample collection for Day -2 will start approx. at 06:30 AM on Day -2 after the first morning void which should be discarded and will end after 24 hours ±1 hour on Day -1

From Day -1 on, the 24-hour urine collection for the respective day will immediately start after the end of 24-hour urine collection of the previous day (after 24 hours ± 1 hour) (Appendix A). After nearly 24-hours of urine collection, subjects will empty their bladder again and this urine will be used as the final portion of the 24-hour urine sample. During the collection period, all urine passed must be collected and put into the sampling container, with the exception of about 10 mL for the spot urine tests (described above). The spot urine sample of the amount of 10 mL for the urine pregnancy test and safety urine analysis will be taken from the final portion of the 24-hour urine sample before putting this final portion into the sampling container. The amount of 10 mL for the spot urine tests should not be subtracted from the 24-hour urine

sample. No urine must be passed into the toilet. The start and the end time of urine collection will be recorded by the subject in a form and checked by the site collaborators. The volume of 24-hour urine will be measured by the site collaborators upon collection of urine containers from the subjects.

For assessment of urine BoExp, creatinine for normalization of urine BoExp, sample bio-banking and urine mutagenicity, aliquots from the 24-hour urine collection will be taken. In the schedule of events for the 24-hour urine collection (see Appendix A) the dot corresponds to the day on which the 24-hour urine collection period starts. For example, NEQ measured at Day 5 in the 24-hour urine collection starts on Day 5 and ends in the morning of Day 6 prior to Discharge.

For the Discharge on Day 6, subjects will empty their bladder shortly before 06:29 AM. This will be the last urine portion for the 24-hour urine for the Day 5 dot mark in the schedule of events. The spot urine sample of the amount of 10 mL for the urine pregnancy test and safety urine analysis will be taken from the final portion of the 24-hour urine sample before putting this final portion into the sampling container. The amount of 10 mL for the spot urine tests should not be subtracted from the 24-hour urine sample. For assessment of urine BoExp, creatinine, and samples for bio-banking (if consent received, 5 tubes of urine will be taken for bio-banking), aliquots from the 24-hour urine collection will be taken. In the schedule for 24-hour urine collection assessments, the dot corresponds to the day on which the 24-hour urine collection period ends.

See Appendix A for the timepoints of assessment.

7.6.3 Bio-Banking for Long-Term Storage of Blood and Urine

If a subject gives consent for sample bio-banking for long-term storage, additional samples of urine (from the 24-hour urine collection) and serum/plasma (20 mL of blood in total) will be collected as follows:

- Samples from the 24-hour urine will be collected from the urine collections that started on Day -1 and on Day 5, respectively.
- Serum/plasma will be collected on Day -1 and Day 6.

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

If a subject gives consent for sample bio-banking of whole blood/plasma for further transcriptomics and plasma for lipidomics analysis, an additional 10 mL of blood will be collected for each assessment: 5 mL for transcriptomics will be aliquoted in 2 tubes (2.5 mL of blood/tube); for lipidomics, the 4 mL of blood will be centrifuged and the plasma aliquoted in 4 tubes of 500 µl each.

The samples intended for sample bio-banking will be kept frozen and shipped to a central storage facility. After the final CSR is signed, samples of plasma/serum/blood will be stored for a maximal period of 5 years and samples of urine will be stored for a maximal period of 2 years. The blood/plasma bio-banking for transcriptomics and lipidomics will be stored for a maximum period of 5 years.

If a subject withdraws his/her consent for sample bio-banking the facility at which the samples are stored will follow their procedures for destruction of banked samples as stated in section 7.6.3.

See Appendix A for the timepoints of assessment.

7.7 Other Study Procedures

7.7.1 Human Puffing Topography Assessment

Human puffing topography involves the measurement of each smoker's unique way of smoking CCs or using CHTP 1.0 using the HPT SODIM® device. The HPT SODIM® device, model SPA/M (SODIM® Instrumentation, Fleury les Aubrais, France) is a device which is used to measure puffing topography (see Appendix C). It consists of a special sample holder (containing a constriction in the middle) which is placed between the subject's mouth and the filter of the CC or CHTP 1.0 being smoked/used. The sample holder is connected by 2 narrow tubes to a portable data logger/recording system (see Appendix C for a description of the device). Any malfunction of the HPT SODIM® portable device will be documented in appropriate log.

At Day -2, the HPT SODIM® device has to be used for all CC smoked for all subjects. On Day 1 and Day 4 of the confinement period, the HPT SODIM® device has to be used for every product use for all subjects in the CC and CHTP 1.0 arms.

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

For each subject, one HPT Device (configured for CC use) will be assigned at Day -2 which will be used by that subject on all HPT assessments days during baseline. Then, at Day 1, subjects randomized to the CC arm will still use the same HPT Device that was used during baseline whereas new HPT Devices (configured for CHTP 1.0 use) will be assigned for subjects randomized in the CHTP 1.0 arm.

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

7.7.2 Human Puffing Topography Parameters

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

Prior to calculation of the per-CHTP 1.0/CC parameters, the Sponsor's HPT group will validate the data and discard any invalid data. Only valid data for the per-CHTP/cigarette parameters will be part of the study database and will be analyzed.

Table 4 Human Puffing Topography – Per-Puff Parameters

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	ml
Puff duration	Di	s
Average flow [Vi/Di]	Qmi	ml/s
Peak flow	Qci	ml/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Work [INT Pmi*FinalFlow*dt]	Wi	mJ
Average pressure drop	Pmi	mmWG
Peak pressure drop	Pci	mmWG
Average resistance [Pmi/Qmi]	Rmi	mmWG/ml/s
Peak resistance [Pci/Qci]	Rci	mmWG/ml/s

Table 5 Human Puffing Topography – Per-CHTP 1.0/Cigarette Parameters

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

Description	Variable	Formula	Unit
Total inter puff interval	TIi	Σ Ii	s
Average inter puff interval	AvgIi	Σ Qci / NPC, i=1 … NPC	s
Total smoking duration	TDFi	Σ DFi	s
Total work	TWi	Σ Wi	mJ
Average work	AvgWi	Σ Wi / NPC, i=1 … NPC	mJ
Average pressure drop	AvgPmi	Σ Pmi / NPC, i=1 … NPC	mmWg
Average peak pressure drop	AvgPci	Σ Pci / NPC, i=1 … NPC	mmWg
Puffing intensity	SMINT	TVOL/TDFi	ml/s
Puffing time index	PTI	(100*TDi)/TDFi	%
Puff frequency	PFeq	NPC/(TDFi/60)	Min^{-1}

7.7.3 CHTP Plug and Diffuser Analysis

All CHTPs 1.0 used on Day 4 will be collected and sent to an external laboratory for analysis of smoke nicotine in the plug and diffuser.

7.7.4 Handling and Collection of CHTPs 1.0 after use on Day 4

- Right after the end of using a CHTP 1.0 on Day 4, the used CHTP 1.0 will be inserted into the glass tube provided with the heat source oriented to the bottom of the glass tube. The extinguisher must not be used beforehand.
- The glass tube is then placed in the glass tube holder to let CHTP 1.0 used cooling down.
- Within 12 hours after the CHTP 1.0 collection, the combi filter will be manually separated from the rest of CHTP 1.0 by applying an appropriate bending force (between the diffuser and the polymer-film filter [PLA] section).
- Close the tube with a yellow cap and store the tubes at 4 ± 3°C until shipment.

Further details will be provided in the site manual.

7.8 Questionnaires

The subject questionnaires and the cough-VAS used in this study will be answered and assessed by the subject directly on paper copy. All subject-reported outcome data as well as instructions will be provided in the subject's local language. The questionnaires and the cough-VAS will be viewed for completeness by the site collaborators and subjects will be requested to complete any missing information.

Symptoms or worsening of symptoms documented on any of the questionnaires or on the VAS do not need to be documented as additional AEs because the questionnaires and the cough-VAS will be analyzed as part of the final report. However, it is at the discretion of the Investigator or designee to decide whether to document such symptoms as additional AEs. The main source for AE collection will be the face-to-face interview between the subject and the site collaborators, using open, non-directive questions (section 8).

See Appendix A for the timepoints of assessment.

The questionnaires should be done at the same time for each visit.

7.8.1 Fagerström Test for Nicotine Dependence (Revised Version)

Potential nicotine dependence will be assessed via a subject self-reported questionnaire using the Fagerström test for nicotine dependence (FTND) in its revised version [17].

The questionnaire consists of six questions which will be answered by the subject himself/herself. The scores obtained on the test allow the classification of nicotine dependence in three different levels: mild (0-3 points), moderate (4-6 points), and severe (7-10 points).

See Appendix A for the timepoints of assessment.

7.8.2 Assessment of Cough-VAS

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 will be conducted irrespective of the time.

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

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

Furthermore, subjects will assess the intensity and frequency of cough and the amount of sputum production during the previous 24 hours on Likert scales.

The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = very mild – 2 = mild – 3 = moderate – 4 = severe – 5 = very severe.

The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = rarely – 2 = sometimes – 3 = fairly often – 4 = often – 5 = almost always.

The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3, with 0 = no sputum – 1 = a moderate amount of sputum – 2 = a larger amount of sputum – 3 = a very large amount of sputum.

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

See Appendix A for the timepoints of assessment.

7.8.3 Modified Cigarette Evaluation Questionnaire (MCEQ, Modified Version)

Product evaluation will be assessed using the subject self-reported MCEQ [18]. The MCEQ assesses the degree to which subjects experience the reinforcing effects of smoking, by measuring:

- Smoking satisfaction (satisfying, tastes good, enjoy smoking).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nauseous).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

See Appendix A for the timepoints of assessment.

7.8.4 Human Puffing Topography Questionnaire (HPT Questionnaire)

A specific subject self-reported questionnaire, used for exploratory purposes, has been developed by PMI to evaluate the impact of the utilization of the HPT SODIM® device on smoker's puffing experience in terms of ritual disruption. This is a questionnaire with 5 items to be rated on a 5-point scale and open questions. Subjects will be asked by the Investigator or designee to complete the HPT questionnaire at:

- On Day -2, HPT and HPT questionnaire will be done in all subjects using CC compatible with the HST SODIM®
- On Day 1 and Day 4 in the confinement period, HPT and HPT questionnaire will be done in all subjects in the CHTP 1.0 and CC arms. Puffing topography with the HPT SODIM® device will not be done in subjects using CC that are incompatible with the HPT SODIM® device (*e.g.*, slim CC).

See Appendix A for the timepoints of assessment.

7.8.5 Questionnaire of Smoking Urges

To assess the urge-to-smoke, all subjects will be asked to complete a 10-item brief version of the QSU [19]. The QSU-brief is a subject self-reported questionnaire with 10 items to be rated

on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicate a higher urge-to-smoke.

The findings in this brief version were consistent with the expressions of craving found in the 32-item version of the QSU [20]. The findings supported a multi dimensional conceptualization of craving to smoke and demonstrated the utility of a brief multi-dimensional measure of craving [19].

See Appendix A for the timepoints of assessment.

7.8.6 Minnesota Nicotine Withdrawal Scale (Revised Version)

The MNWS revised version is a valid and reliable subject self-reported scale that has been used previously to examine signs and symptoms of withdrawal from cigarette smoking [21, 22]. It consists of 2 scales: a ”self-report scale’ and an ‘observer scale.”

For the purpose of this study, only the self-reporting scale will be used and filled-in by the subject. Furthermore, the subject’s weight will not be recorded for the purpose of the MNWS. At the end of the assessment of the questionnaire, the subject’s pulse rate will be recorded.

Subjects will be asked to rate the items for the previous 24 hours on a scale ranging from 0 to 4 (where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe).

See Appendix A for the timepoints of assessment.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

According to ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [23]), an AE is defined as any untoward medical occurrence in a subject administered an IP or reference product, which does not necessarily have a causal relationship with the IP or reference product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP or reference product, whether or not it is considered related to the IP or reference product.

The FDA MRTP guideline specifies the following definition for adverse events for tobacco products [4].

An AE is any health-related event associated with the use of a tobacco product in humans, which is adverse or unfavorable, whether or not it is considered related to the tobacco product. An AE can arise from any use of the product (including use in combination with other products and overdose).

8.1.2 Serious Adverse Events

A SAE is defined as, but is not limited to, any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE, when, based on appropriate medical judgment, an SAE may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

Any pre-planned hospitalizations that are known at the time of signing the ICF will not be recorded as an SAE; however they will be recorded as AE only. Any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

8.2 Assessment of Adverse Events

The Investigator or designee is responsible for obtaining, assessing and documenting all AEs during the study.

8.2.1 Collection of Information

Adverse event information will be collected from the time of signature of the ICF onwards until EOS either by the Investigator or designee via spontaneous reporting or by the use of consistent, open, non-directive questions from site collaborators (*e.g.*, "Have you had any health problems since the previous visit/How are you feeling since you were last asked?"). The main source for AE collection will be face-to-face interview(s) with the subject.

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

For each AE, the intensity will be graded on a 3-point intensity scale (mild, moderate, severe) using the definitions provided in section 8.2.3.

Any exacerbation/worsening or increased frequency of an AE or pre-existing condition shall be evaluated and recorded.

Correct medical terminology/concepts are preferred when recording AE terms, and abbreviations must be avoided. Wherever possible, a diagnosis is to be used to describe an AE as a diagnosed medical condition rather than individual signs and symptoms (*e.g.*, record 'pneumonia' rather than 'fever', 'cough', 'pulmonary infiltrate' or 'anemia' rather than 'decreased hemoglobin').

Any AE that meets the seriousness criteria must be recorded both on the AE report form of the CRF and on a separate SAE report form (section 8.3).

8.2.2 Period of Collection

From the time of signature of the ICF onwards until EOS, all AEs (includes SAEs) will be collected by the site collaborators as described below.

Medical history is defined as any condition that started and ended prior to the Screening Visit. A concomitant disease is defined as any condition that started after ICF signature or was started prior to the Screening Visit and is still ongoing at the Screening Visit. Relevant medical history and any concomitant disease will be documented at the Screening Visit.

8.2.2.1 Screening Period

Any AEs which occur during the Screening Period will be captured by the site collaborators and assessed by the Investigator or designee in order to establish relationship or relatedness in

respect to study procedures. All collected AEs will be reported in the CSR and will be in accordance with the respective regulatory guidelines.

8.2.2.2 Admission until End of the Study

From Admission onwards until Discharge, all AEs will be actively collected by the site collaborators.

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

During the Safety Follow-up Period AEs and/or SAEs will be recorded after reporting by the subject. SAEs will be reported by the Investigator as described in this document and the safety management plan (SMP). Any ongoing AEs during the Safety Follow-up Period will be followed up by the site. All AEs will be followed-up until they have been resolved, stabilized (*i.e.*, no worsening of condition), or an acceptable explanation has been found until the end of the Safety Follow-up Period. Within 3 days after the end of the Safety Follow-up Period the investigator will attempt to contact the subjects by phone to check for if all AEs/SAEs potentially occurring during the Safety Follow-up period are fully reported.

At the end of the Safety Follow-up Period, all ongoing AEs will be documented as "ongoing" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner for follow-up on ongoing AEs.

8.2.3 Intensity of Adverse Event

For each AE, the intensity will be evaluated by the Investigator or designee on a 3-point intensity scale (mild, moderate, severe) using the following definitions:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and requires medical intervention.

Change in severity (intensity) needs to be documented.

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

It is difficult to establish a firm method to distinguish an adverse reaction (that is AE that is causally related to the IP) from a clinical AE that is temporally associated to the use of an IP. In general, all AEs and/or SAEs will be assessed by the Investigator as either 'related' or 'not related' to IP or reference product as described below. In addition to the assessment of the

relationship of the clinical event to the IP, the Investigator shall document a potential relationship of the clinical event to any particular study procedure.

Not related: The temporal relationship of the clinical event to IP or reference product administration makes a causal relationship unlikely, or concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Related: The temporal relationship of the clinical event to study IP or reference product administration makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP CHTP 1.0 will be assessed for its expectedness. An AE will be regarded as 'unexpected' if its nature or severity is not consistent with information already known about the IP, and is not listed in the current IB. The IB provides further detail on signs or symptoms that might be expected with the use of the IP, including information relating to malfunction or misuse.

8.3 Reporting of Serious Adverse Events

Any SAEs reported or observed during the study after signature of the ICF until EOS, whether or not attributable the IP, or to any study procedures, or any SAE related to the product and spontaneously reported after the Safety Follow-up must be reported by the Investigator or other site collaborators **within 24 hours after first awareness by any party involved in the study** to [redacted] and to the Sponsor.

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

[redacted]**Safety:**	**Fax number:**	+41 [redacted]
	E-mail:	[redacted]
	Address:	[redacted]

Sponsor Contact:	**Phone:**	+41 [redacted]
[redacted]	**E-mail 1:**	[redacted]pmi.com
	E-mail 2:	[redacted].pmi.com
	Address:	Philip Morris Products S.A. R&D Innovation Cube Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

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

Any SAE will be reported to the competent authorities by the Sponsor as per local requirements.

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

The follow-up SAE report form must include the minimum information required as described in the safety management plan for form completion and only modified or new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

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

The SAE report form to be used in this study is provided as a separate document and included in the study master file. All SAEs will be recorded in the CRF, in addition to the SAE report form.

8.4 Reporting of Other Events Critical to Safety Evaluations

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator or designee and assessed for clinical relevance. If an abnormal laboratory result is detected after Screening and considered clinically relevant (see below), this should be recorded as an AE.

The grading scheme shown in Appendix E will be used by the Investigator or designee to assess abnormal laboratory AEs as follows:

- All grade 1 abnormal laboratory values will be evaluated by the Investigator or designee with respect to baseline value and clinical relevance. If considered to be clinically relevant the Investigator or designee must report it as an AE. All grade 2 and higher abnormal laboratory values must be reported as, or linked to, an AE/concomitant disease.
- If a subject has grade 2 and higher abnormal laboratory values at V1 it is at the discretion of the Investigator or designee to enroll the subject or not. This decision must be documented in the source document and captured in the CRF. A grade 2 laboratory abnormal value at V1 must be recorded as concomitant disease.
- If there is any worsening in grade from grade 2 and above during the study the Investigator or designee must report this worsening as an AE.
- Where there is no grading available, the abnormal laboratory value will be evaluated by the Investigator or designee and assessed for clinical relevance. If considered to be clinically relevant, the Investigator will report it as an AE.
- Any other abnormal clinical laboratory result (including those that are not part of the core safety assessments) can, at the discretion of the Investigator or designee, be reviewed and assessed. Even if they do not meet the criteria of the CTCAE grading scheme (please see above), the Investigator or designee may consider them to be of clinical relevance and, if they are, must report them as AEs.
- In general, laboratory values will be recorded as 'increased <lab parameter>' or 'decreased <lab parameter>' to ensure consistency of recording/coding.

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

8.5 Reporting and Follow-Up of Pregnancies

For pregnancies detected between the time point of signature of the ICF to the enrolment of the subject, the subject will be considered as a screen failure and removed from the study. No pregnancy form will be filled, however the diagnosed pregnancy must be captured in the screen failure CRF.

Any pregnancy that occurred after first exposure to the IP and is potentially associated with exposure to the IP, including pregnancies spontaneously reported to the Investigator or designee after the EOS must be reported by the Investigator and followed-up until the pregnancy outcome is reached.

Potential association with exposure to the IP is defined as the conception date being calculated to have been before the date of the last IP exposure.

The Investigator will complete a pregnancy form (provided as a separate document) for all pregnancies diagnosed (including positive urine pregnancy tests).

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

[redacted] will follow up pregnancies only if they were detected after first product use (*i.e.*, after CHTP 1.0 test at Admission). If pregnancies are to be followed-up, they will be followed-up until an outcome is reached (*e.g.*, normal delivery, spontaneous abortion, or voluntary termination). Any pregnancy complication, adverse pregnancy outcome, or maternal complications will be recorded.

The Principal Investigator or designee is responsible for informing the IRB of any pregnancy that occurs during the study and its outcome, according to local regulations.

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE, will undergo the early termination procedures as described in section 9.4 as soon as possible. The Investigator or designee and/or [redacted] will follow up these AEs until they have been resolved, stabilized (*i.e.*, no worsening of condition), or until an acceptable explanation has been found.

8.7 Investigational Product Malfunction and Misuse

Any occurrences of CHTP 1.0 malfunction ([redacted]) or misuse (use not in accordance with its label and instruction) by a subject, will be documented by the Investigator or his/her designated collaborator using a product issue log provided by the sponsor.

Investigational product misuse may result in use-related hazards.

Furthermore, any misuse or malfunction of CHTP 1.0 that lead to an AE/SAE will follow the same processes as described above for the reporting of an AE/SAE.

9 STUDY ACTIVITIES

A detailed schedule of assessments can be found in Appendix A.

The time points shown are to be considered the time of assessment for the first subject. As not all subjects can be treated at the same time, a short time window will be implemented for subsequent subjects. Measurements not conducted at the exact time point, but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given time point.

In general, if no start time for the procedure is provided, then the procedure can be performed at any time during the day.

9.1 Screening Visit

The Screening Visit will be performed within 6 weeks (1 to 42 days) prior to Admission. First, the ICF along with study information should be given to the subject. When/if the ICF is signed, dated and timed, the other screening procedures can be performed in the order deemed most practical. The point of time of each screening procedure must be recorded in the source document. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed during the Screening Visit.

Table 6 shows the procedures for the Screening Visit. The sequence of assessments/events is given just for illustrative purposes and will be at the discretion of the site after signature of the ICF.

Table 6 Time Schedule – Screening Visit (Day -45 to Day -3)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Screening**	
Before any study procedure		Informed consent for study participation and additional consents for bio-banking (if applicable)	
During the visit	√	Clinical laboratory parameters (hematology, clinical chemistry)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Screening**	
During the visit	√	Serology (HIV, hepatitis B and C)	
During the visit		Information on the risks of smoking, smoking cessation advice and debriefing.	
During the visit		Demographic data collected	
During the visit		Questions about smoking history/habits and Intention to quit smoking	
During the visit		Medical history/concomitant disease, prior and concomitant medication	
During the visit		Identification of currently used CC brand	
During the visit		FTND questionnaire	
During the visit		ECG	At least 10 minutes in supine position prior to recording
During the visit		Chest X-ray	If not performed 6 months prior to Screening
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
During the visit		Safety urine analysis	
During the visit		Urine pregnancy test (females only)	
During the visit		Physical examination, height and weight	
During the visit		Urine drug screening	
During the visit		Urine cotinine screening	
During the visit		Alcohol breath test	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Screening**	
During the visit		Spirometry pre- and post-bronchodilatator (recording of FEV_1, FVC, FEV_1/FVC)	Has to be done at least 1 hour after having stopped smoking At rest in sitting position for at least 15 minutes prior to pulmonary function testing. In sitting position. All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of salbutamol
During the visit		AE/SAE recording	If the Screening Visit is performed on two separate days, the AE/SAE questions will be asked again
During the visit		Inclusion/exclusion criteria	
During the visit		CHTP 1.0 product demonstration	

Abbreviations: AE = Adverse event; CC = Conventional cigarette; CHTP 1.0 = Carbon Heated Tobacco Product 1.0; ECG = Electrocardiogram; FEV_1= Force expiratory volume in 1 second; FVC = Forced vital capacity; FTND = Fagerström test for nicotine dependence; HIV = Human immunodeficiency virus; SAE = Serious adverse event.

9.2 Confinement Period (Day -3 to Day 6)

9.2.1 Admission (Day -3)

The procedures of Day -3 can be performed in order deemed most practical. Table 7 shows the assessments that will be performed on the day of Admission (Day -3).

Table 7 Time Schedule – Admission (Day -3)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Admission (Day -3)**	
During the visit		Urine drug screening	Prior to Enrolment
During the visit		Urine cotinine screening	Prior to Enrolment
During the visit		Urine pregrancy test (female only)	Prior to Enrolment
During the visit		Alcohol breath test	Prior to Enrolment
During the visit		Information on the risks of smoking, smoking cessation advice and debriefing.	Prior to Enrolment
During the visit		Prior/concomitant medication	Prior to Enrolment
During the visit		Questions about smoking history/habits and intention to quit smoking	Prior to Enrolment
During the visit		Identification of currently used CC brand	Prior to Enrolment
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position Prior to Enrolment
During the visit		Physical examination, body weight, and calculated BMI	Prior to Enrolment
During the visit		Inclusion/exclusion criteria	All eligibility criteria must be checked.
During the visit		Enrolment	
		Product test for CHTP 1.0 (Use of up to 5 sticks of CHTP 1.0)	After enrolment. Subjects who are unwilling to use the product for 5 days will be discontinued from the study CHTP 1.0 used will be collected for accountability.
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		Collection of used CC butts	For accountability

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Admission (Day -3)**	

Abbreviations: AE = Adverse event; BMI = Body mass index; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; SAE = Serious adverse event.

9.2.2 Baseline Period (Day -2 and Day -1)

Table 8 and Table 9 show the assessments that will be performed on Day -2 and Day -1, respectively.

The collection of 24-hour urine sample for Day -2 will start in the morning of Day -2 and will end in the morning of Day -1.

The collection of 24-hour urine sample for Day -1 will start in the morning of Day -1 and will end in the morning of Day 1.

Table 8 Time Schedule – Day -2

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -2)**	
6:30 AM		Start of smoking CC	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		Start of 24-hour urine sample collection for Day -2.	The start of urine collection should start after the first morning void which should be discarded, and the end is in the morning of the following day.
06:30 AM - 09:30 AM		Start of HPT assessment	The HPT SODIM® device has to be used for all smoking events when compatible CCs are smoked.
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling.
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test.
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required.
8:00 PM - 11:00 PM		Craving questionnaire (QSU brief)	
8:00 PM - 11:00 PM		Product evaluation questionnaire (MCEQ)	
8:00 PM - 11:00 PM		HPT questionnaire	
11:00 PM		End of smoking period	
6:30 AM - 11:15 PM		Collection of used CC butts	For accountability

Abbreviations: AE = Adverse event; CC = Conventional cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; QSU–brief = Questionnaire of smoking urges (brief version); MCEQ = Modified cigarette evaluation questionnaire; SAE = Serious adverse event.

Table 9 Time Schedule – Day -1

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -1)**	
6:30 AM		Start of smoking	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day -2	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to smoking the first CC.
		Start of 24-hour urine sample collection for Day -1.	The start of 24-hour urine collection of Day -1 should be subsequent to the end of 24-hour urine collection of Day -2
		Urine sample to be taken from the 24-hour urine of Day -2.	Aliquots from 24-hour urine will be collected according to Table A2.
Prior to 11:30 AM	√	CYP2A6 activity in plasma	Has to be done early in the morning prior smoking
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Prior to 11:30 AM		MNWS questionnaire	Has to be done prior to smoking
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to smoking

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -1)**	
Prior to 11:30 AM		Spirometry pre- and post-bronchodilatator (recording of FEV_1, FVC, FEV_1/FVC)	Has to be done before smoking At rest in sitting position for at least 15 minutes prior to pulmonary function testing. In sitting position. All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of salbutamol
Prior to 11:30 AM	√	Bio-banking for biomarkers and transcriptomics and lipidomics	If additional consent is signed. After at least 10 hours of fasting
Prior to 11:30 AM	√	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 10 hours of fasting
Prior to 11:30 AM		Safety urine analysis	
Prior to 11:30 AM		Intake of a cup of coffee made from 4.2 g (±10%) regular instant coffee; CAF content: 72 mg/2 g) with 150 ml ±10 ml water.	The time of intake of the cup of coffee must be recorded
04:00 PM - 06:00 PM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the the cup of coffee .
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling.
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test.
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -1)**	
8:00 PM-11:00 PM		Craving questionnaire (QSU brief)	
8:00 PM-11:00 PM		Product evaluation questionnaire (MCEQ)	
11:00 PM		End of smoking period	
6:30 AM-11:15 PM		Collection of used CC butts	For accountability
		Randomization	Day -1

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; CYP2A6 = Cytochrome P450 2A6; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event

9.2.3 Exposure Period (Days 1 to 5)

Table 10 shows the assessments that will be performed on Day 1.

The collection of 24-hour urine of Day -1 starting on Day -1 will end on Day 1.

The collection of 24-hour urine sample for Day 1 will start on Day 1 and will end on Day 2.

Table 10 Time Schedule – Day 1

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
6:30 AM		Start of use of IPs	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day -1	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to first use of IPs.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
		Start of 24-hour urine sample collection for Day 1.	The start of 24-hour urine collection of Day 1 should be subsequent to the end of 24-hour urine collection of Day -1.
		Urine sample to be taken from the 24-hour urine of Day -1	Aliquots from 24-hour urine will be collected according to Table A2.
			Bio-banking for biomarkers (if additional consent is obtained)
06:30 AM - 09:30 AM		Start of HPT assessment	In both study arms CHTP 1.0 and CC, the HPT SODIM® device has to be used for all smoking events when compatible CCs are smoked
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Prior to 11:30 AM		MNWS questionnaire	Has to be done prior to use of IPs
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to use of IPs
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
8:00 PM - 11:00 PM		Craving questionnaire (QSU brief)	
8:00 PM - 11:00 PM		Product evaluation questionnaire (MCEQ)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
8:00 PM - 11:00 PM		HPT questionnaire	
11:00 PM		End of use of IPs	
6:30 AM - 11:15 PM		Collection of used CC butts	For accountability
6:30 AM - 11:15 PM		Collection of used CHTP 1.0	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; CYP2A6 = Cytochrome P450 2A6; HPT = Human puffing topography; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event

Table 11 shows the assessments that will be performed on Day 2.

The collection of 24-hour urine of Day 1 starting on Day 1 will end on Day 2.

The collection of 24-hour urine sample for Day 2 will start on Day 2 and will end on Day 3.

Table 11 Time Schedule - Day 2

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 2**	
6:30 AM		Start of use of IPs	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day 1	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to first use of IPs.
		Start of 24-hour urine sample collection for Day 2.	The start of 24-hour urine collection of Day 2 should be subsequent to the end of 24-hour urine collection of Day 1

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 2**	
		Urine sample to be taken from the 24-hour urine of Day 1	Aliquots from 24-hour urine will be collected according to Table A2.
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Prior to 11:30 AM		MNWS questionnaire	Has to be done prior to use of IPs
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to use of IPs
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
8:00 PM - 11:00 PM		Craving questionnaire (QSU brief)	
8:00 PM - 11:00 PM		Product evaluation questionnaire (MCEQ)	
11:00 PM		End of use of IPs	
6:30 AM - 11:15 PM		Collection of used CC butts	For accountability
6:30 AM - 11:15 PM		Collection of used CHTP 1.0	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event

Table 12 shows the assessments that will be performed on Day 3.

The collection of 24-hour urine of Day 2 starting on Day 2 will end on Day 3.

The collection of 24-hour urine sample for Day 3 will start on Day 3 and will end on Day 4.

Table 12 Time Schedule - Day 3

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 3**	
6:30 AM		Start of use of IPs	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day 2	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to first use of IPs.
		Start of 24-hour urine sample collection of Day 3.	The start of 24-hour urine collection of Day 2 should be subsequent to the end of 24-hour urine collection of Day 2
		Urine sample to be taken from the 24-hour urine of Day 2	Aliquots from 24-hour urine will be collected according to Table A2.
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Prior to 11:30 AM		MNWS questionnaire	Has to be done prior to use of IPs.
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to use of IPs.
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
8:00 PM - 11:00 PM		Craving questionnaire (QSU brief)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 3**	
8:00 PM - 11:00 PM		Product evaluation questionnaire (MCEQ)	
11:00 PM		End of use of IPs	
6:30 AM - 11:15 PM		Collection of used CC butts	For accountability
6:30 AM - 11:15 PM		Collection of used CHTP 1.0	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event

Table 13 shows the assessments that will be performed on Day 4.

The collection of 24-hour urine of Day 3 starting on Day 3 will end on Day 4.

The collection of 24-hour urine sample for Day 4 will start on Day 4 and will end on Day 5.

Table 13 Time Schedule - Day 4

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 4**	
6:30 AM		Start of use of IPs	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day 3	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to first use of IPs.
		Start of 24-hour urine sample collection of Day 4.	The start of 24-hour urine collection of Day 2 should be subsequent to the end of 24-hour urine collection of Day 3

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 4**	
		Urine sample to be taken from the 24-hour urine of Day 3.	Aliquots from 24-hour urine will be collected according to Table A2.
06:30 AM - 09:30 AM		Start of HPT assessment	In both study arms CHTP 1.0 and CC, the HPT SODIM® device has to be used for all smoking events when compatible CCs are smoked
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Prior to 11:30 AM		MNWS questionnaire	Has to be done prior to use of IPs.
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior touse of IPs.
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
8:00 PM - 11:00 PM		Craving questionnaire (QSU brief)	
8:00 PM - 11:00 PM		Product evaluation questionnaire (MCEQ)	
8:00 PM - 11:00 PM		HPT questionnaire	
11:00 PM		End of use of IPs.	
6:30 AM - 11:15 PM		Collection of used CC butts	For accountability
6:30 AM - 11:15 PM		Collection of used CHTP 1.0	For accountability and plug and diffuser analysis

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 4**	

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event

Table 14 shows the assessments that will be performed on Day 5.

The collection of 24-hour urine of Day 4 starting on Day 4 will end on Day 5.

The collection of 24-hour urine sample for Day 5 will start on Day 5 and will end on Day 6.

Table 14 Time Schedule - Day 5

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 5**	
6:30 AM		Start of use of IPs	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day 4	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to first use of IPs.
			BoExp (for primary and secondary endpoints, NEQ) and creatinine in 24-hour urine
		Start of 24-hour urine sample collection of Day 5.	The start of 24-hour urine collection of Day 5 should be subsequent to the end of 24-hour urine collection of Day 4
		Urine sample to be taken from the 24-hour urine of Day 4	Aliquots from 24-hour urine will be collected according to Table A2.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 5**	
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Prior to 11:30 AM		MNWS questionnaire	Has to be done prior to use of IPs
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to use of IPs
Prior to 11:30 AM		Intake of a cup of coffee made from 4.2 g (±10%) regular instant coffee; CAF content: 72 mg/2 g) with 150 ml ±10 ml water.	The time of intake of the cup of coffee must be recorded
04:00 PM - 06:00 PM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the cup of coffee
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)		CO breath test	Has to be done in conjunction with COHb blood sampling
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	COHb in blood	Has to be done in conjunction with CO breath test
In the evening prior to 9:00 PM (approx. 8:00 PM ± 1 hour)	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
8:00 PM - 11:00 PM		Craving questionnaire (QSU brief)	
8:00 PM - 11:00 PM		Product evaluation questionnaire (MCEQ)	
11:00 PM		End of use of IPs	
6:30 AM - 11:15 PM		Collection of used CC butts	For accountability
6:30 AM - 11:15 PM		Collection of used CHTP 1.0	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CHTP 1.0 = Carbon Heated Tobacco Product 1.0; CO = Carbon monoxide; COHb = Carboxyhemoglobin; MCEQ = Modified cigarette evaluation questionnaire; MNWS = Minnesota nicotine withdrawal scale (revised version); QSU–brief = Questionnaire of smoking urges (brief version); SAE = Serious adverse event

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

The collection of 24-hour urine of Day 5 starting on Day 5 will end on Day 6.

Table 15 Time Schedule - Day of Discharge (Day 6)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 6**	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
		End of 24-hour urine sample collection for Day 5	The urine is collected for 24 hours ±1 hour.
		Urine sample to be taken from the 24-hour urine of Day 5	Aliquots from 24-hour urine will be collected according to Table A2.
			Bio-banking for biomarkers (if additional consent is obtained)
06:29 AM ±30 min	√	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 10 hours of fasting
06:29 AM ±30 min	√	CYP2A6 activity in plasma	Has to be done before smoking
Before Discharge		Spirometry pre- and post-bronchodilatator (recording of FEV_1, FVC, FEV_1/FVC)	Has to be done before smoking
			At rest in sitting position for at least 15 minutes prior to pulmonary function testing
			In sitting position
			All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of salbutamol
06:29 AM ± 1 hour		MNWS questionnaire	
06:29 AM ± 1 hour		Assessment of cough (VAS)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 6**	
Prior to 11:30 AM	√	Bio-banking for biomarkers, transcriptomics and lipidomics	If additional consent is signed After at least 10 hours of fasting
Before Discharge		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
Before Discharge		Physical examination, body weight, and calculated BMI	
Before Discharge		Safety urine analysis	
Before Discharge		Urine pregnancy test (females only)	
Before Discharge		ECG	At least 10 minutes in supine position prior to recording
Before Discharge		Information on the risks of smoking, smoking cessation advice and debriefing.	
		Discharge	

Abbreviations: AE = Adverse event; BMI = Body mass index; BoExp = Biomarker (s) of exposure; CC = Conventional cigarette(s); CYP2A6 = Cytochrome P450 2A6; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; MNWS = Minnesota nicotine withdrawal scale (revised version); SAE = Serious adverse event

9.3 Safety Follow-Up Period

All subjects participating in the product test on Day -3 will enter the 7 days for the Safety Follow-up Period.

After Discharge on Day 6 (or if prematurely discontinued from the study), the subject will enter a 7-day Safety Follow up Period during which the follow-up of ongoing AEs/SAEs will be done by the study site. All AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the Safety Follow-up Period. Within 3 days after the end of the Safety Follow-up Period the investigator will attempt to contact the subjects by phone to check for if all AEs/SAEs potentially occurring during the Safety Follow-up period are fully reported.

Any AEs or SAEs that are ongoing at the end of the 7 days of the Safety Follow-up Period will be managed as described in section 8.2.2.2.

9.4 Early Termination Procedures

Early termination procedures will be as follows, if the subject agrees:

Table 16 Time Schedule - Early Termination Procedures

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Early Termination**	
		AE/SAE recording	At any time of the day
		Concomitant medications	At any time of the day
	√	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 10 hours of fasting
		Spirometry pre- and post-bronchodilatator (recording of FEV_1, FVC, FEV_1/FVC)	Has to be done 1 hour of not smoking
			At rest in sitting position for at least 15 minutes prior to pulmonary function testing
			In sitting position
			All post-bronchodilator spirometry testing will be performed 15 - 30 minutes post administration of salbutamol
		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
		ECG	At least 10 minutes in supine position prior to recording
		Physical examination, body weight, and calculated BMI	
		Safety urine analysis	
		Urine pregnancy test (females only)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Early Termination**	
		Information on the risks of smoking, smoking cessation advice and debriefing. Discharge	

Abbreviations: AE = Adverse event; BMI = Body mass index; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; SAE = Serious adverse event

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

The contract research organization (CRO) Clinical Research Associate ("Monitor") will be responsible for the monitoring of the study. Monitoring will be performed according to the CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

The Investigator or designee shall permit the Monitor to review study data as frequently as considered necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactorily met.

The Investigator or designee shall access medical records for the Monitor in order that entries in the CRFs may be verified. The Investigator or designee, as part of his/her responsibilities, is expected to ensure that the study adheres to GCP requirements.

An Investigator's meeting will be held prior to the site initiation visit. During this meeting, the general training of the study procedures and specific training on selected procedures will be done and documented.

Subsequent to the Investigator's meeting, and before the first subject is screened and included in the study, a site initiation visit will be conducted by the Monitor and, if necessary, with the Sponsor or its authorized representative. The purpose of the site initiation visit is described in the monitoring plan.

During the study, the Monitor will have regular contact with the study site, including interim monitoring visits. The purpose of these visits is described in the monitoring plan.

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

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

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

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

10.2 Training of Collaborators

A formal meeting (Investigator's meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training to the relevant

systems and other study-specific procedures. The activities of this meeting will be described in the monitoring plan.

Further to the Investigator meeting, the Investigator or designee will ensure that appropriate training relevant to the study is provided to all collaborators involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the site collaborators. The Investigator or designee will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

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

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

The Investigator and site collaborators are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative and/or regulatory agencies. By signing this protocol, the Investigator or designee understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All data management activities will be described in details in the data management plan (DMP) and documents specified therein. The electronic systems used, CRF and SRO, to collect subject data will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

With the exception of the SRO data, all results from the clinical assessments will be recorded in the source data file by the Investigator or his authorized designee(s), and then captured in the CRFs at the study site. Trained study personnel will be responsible for capturing the data from the observations, tests and assessments, specified in the protocol, in the source documents and transferring the data to the CRF according to the CRF completion guidelines.

The Investigator or designee has the ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring and available when required. The CRF must be signed by the Investigator or designee to attest that the data contained in the CRF are true and accurate. Any corrections made to source documents and/or CRFs must be recorded, without obscuring the original values, and must be accompanied by the date of change, reason for change and identification of the person making the change. The CRF data will be verified against the source documents at the study site by the Monitor. Instances of missing or unclear data will be discussed with the Investigator or designee for resolution. All SRO questionnaires will be provided to the subject in his/her local language.

11.1.2 Protocol Deviations

Protocol deviations are defined as deviations from the study procedures as defined in this document, 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.

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

and handled as important communication, documented and tracked as protocol deviations, as necessary.

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

11.2 Data Handling

All study data will be managed by the data management team at the CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO data management team. The data management team at the CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the start of data entry. This document will describe, in details, the data management-related procedures and processes.

Data of all subjects enrolled including screening failures and AE during the study (from the time of informed consent to the end of the study of the subject) will be captured in the source documents and all AEs will be entered in the study database (CRF).

All data collected during the study are declared property of the Sponsor, irrespective of the location of the database and the data management CRO.

Additional details are covered in the DMP.

11.2.1 Data Verification

The data will be verified as defined in the DMP and data verification plan. Discrepancy will be generated electronically, and issued as queries to the site, as necessary.

Data queries will be raised for discrepant or missing data. All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

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

Adverse events, concomitant disease, medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Medications:	WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical classification system
CHTP 1.0 issues and/or malfunction:	C54451/Medical Device Problem Codes FDA CDRH [24]

11.2.3 Database Lock

When all outstanding data management issues have been resolved and quality review and cleaning activities are complete, the database or selected data is/are declared soft-locked. Access to change data in the soft-locked database or to change selected data at this time is limited.

After data review by the Sponsor, resolution of all raised queries and QC of the changed data, the database or selected data thereof will be declared locked upon Sponsor approval, as applicable.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the data management and statistical team at the CRO. Any of those changes must be documented in the database log file.

After study completion, the study database will be transferred to the Sponsor in the format specified in the DMP and defined in the data transfer agreement. The clinical database will be provided in the "Clinical Data Interchange Standards Consortium Study Data Tabulation Model Data Structure Specifications".

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

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

The data from this study could be used for the purpose of providing data for the design and interpretation of assessment studies of PMI candidate modified risk tobacco products.

12.1.1 Stratification Criteria

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

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

12.1.2 Definitions for Statistical Data Analysis

Baseline:

Unless specified, baseline is defined as the last available time point prior to Day 1, 06:30 AM.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by product arm and subject, unless otherwise specified.

In general, summary statistics will be stratified by region and sex at Baseline.

Descriptive statistics (number of subjects [n], number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum and maximum for continuous data, including geometric mean and coefficient of variation (CV) for data analyzed in the log scale; frequency counts and percentages for categorical data) will be presented overall and at each time point, where applicable.

For BoExp, the geometric mean and coefficient of variation (CV) will be presented in addition to the mean and SD.

12.1.4 Handling of Missing Values and of Values outside the Detection Limits

Descriptive summaries will be provided for the evaluable data with no imputation.

Missing values for the endpoints analyzed via the mixed model method will not be directly imputed as they are handled within the analysis itself.

Values below the lower limit of quantification (LLOQ) will be imputed using 0.5 x LLOQ. For values above the upper limit of quantification (ULOQ), the ULOQ will be used for calculation and reporting in summary tables. The number of values below LLOQ or above ULOQ will be presented in each summary table. 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 (if no value below LLOQ is present) and maximum (if no value above ULOQ are present) of the observed values.

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

Further details will be provided in the SAP.

12.1.5 Significance Level for Inferential Analysis

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

The primary endpoints will be tested using a multiple testing procedure to preserve the overall alpha level by simultaneously testing the endpoints using a closed procedure with each test performed at an alpha level of 5%. This implies that statistical significance is required for all primary endpoints in order to be able to make confirmatory claims about any of the endpoints.

Full details of this approach will be provided in the SAP.

12.2 Determination of Sample Size and Power Consideration

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

Table 17 describes the expected coefficients of variation (CV) and mean ratios (MR) between CHTP 1.0 and the two control arms based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study that investigated exposure to selected smoke constituents in smokers switching from CC to smoking article cigarettes for 5 days, the YVD-CS01-EU study (ClinicalTrials.gov: ID: NCT00812279) sponsored by PMI.

Table 17. Coefficients of Variation (YVD-CS01-EU study)

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

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

The power to detect a reduction was computed.

Table 18 describes the expected power to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.0 arm compared to the CC arm after 5 days of exposure, with a one sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU, and 80 randomized subjects in a 1:1 ratio (40 in CHTP 1.0 arm and 40 in CC arm).

Table 18. Expected Power (YVD-CS01-EU study assumptions)

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

The test-wise powers to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.0 arm compared to the CC arm after 5 days of exposure, with a one sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU, and 80 randomized subjects in a 1:1 ratio (40 in CHTP 1.0 arm and 40 in CC arm) are described in Error! Reference source not found.

Table 19. Test-Wise Power (YVD-CS01-EU study assumptions)

Parameter	Test-wise power
COHb	88%
3-HPMA	>99%
MHBMA	>99%
S-PMA	>99%

Given the above calculation, the sample size was considered sufficient to have more than 80% power to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.0 arm compared to the CC arm after 5 days of exposure, using a one sided test with 2.5% type I error probability.

12.3 Analysis Populations

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

Safety will be analyzed using the safety population.

12.3.1 Full Analysis Set

The FAS consists of all the randomized subjects who had at least one post-randomization product use experience, if randomized to CHTP 1.0 or CC, and have at least one valid nonsafety assessment (CHTP 1.0, CC).

12.3.2 Per Protocol Population

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

12.3.3 Safety Population

The safety population consists of all the subjects who had at least one exposure to CHTP 1.0 (product test at Admission Day). Subjects in the safety population will be analyzed according to actual exposure.

12.4 Primary Endpoints

12.4.1 Primary Endpoints Analysis Variables

The primary endpoints are:

- MHBMA (concentration adjusted for creatinine in 24-hour urine) on Day 5
- 3-HPMA (concentration adjusted for creatinine in 24-hour urine) on Day 5
- S-PMA (concentration adjusted for creatinine in 24-hour urine) on Day 5
- COHb on Day 5

See section 3.1.

Evaluation criterion:

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

12.4.2 Baseline Comparability

Not applicable.

12.4.3 Descriptive Summary

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

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

12.4.4 Confirmatory Analyses

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

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

- Null hypothesis (H_0): $m1 \geq m2$
- Alternative hypothesis (H_1): $m1 < m2$

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

The transformed data will be analyzed by means of a generalized linear model using product arm as covariate adjusting for the following baseline information: gender, average cigarette consumption over the previous 4 weeks, and baseline value of endpoint. Estimates of differences between groups will be back-transformed to provide relative effects.

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

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

12.5 Secondary Safety Endpoint(s)

See section 3.2.

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

12.5.1 Secondary Endpoint Analysis Variables

See section 3.2.

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

12.5.2 Baseline Comparability

Not applicable.

12.5.3 Descriptive Analysis

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

12.5.4 Safety Analysis

In general, all safety data will be listed and tabulated on the safety population by product arm, using the approach described in section 12.1.3. Safety variables collected during Exposure Period will also be reported by product exposure.

Adverse event data will serve as the primary assessment of safety. Other safety variables monitored in this study include: respiratory symptoms (cough assessment VAS and Likert scales); vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; clinical chemistry, hematology, concomitant medications, and urine analysis safety panel; physical examination.

The number and percentage of subjects with AEs and SAEs will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to withdrawal, AEs leading to death, AEs by relatedness to product exposure, AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

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

12.6 Exploratory Analysis

12.6.1 Exploratory Endpoint Analysis Variables

See section 3.3.

12.6.2 Baseline Comparability

Not applicable.

12.6.3 Descriptive Analysis

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

12.7 Demographics and Baseline Characteristics

Demographic and other Baseline characteristics will be reported for safety population. Summary statistics will be provided by exposure group and stratified by sex and by cigarette consumption. Formal statistical analysis will not be performed on Baseline demographic data.

12.8 Interim Analysis

There are no planned interim analyses.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigator's and Study Administrative Structure

13.1.1 Investigator

Investigator:	[redacted] BioVirtus Research Site Sp. z o.o. [redacted] [redacted] Tel: +48 [redacted] Fax.: +48 [redacted] [redacted]

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland Tel: +41 (58) 242 2111 Fax: +41 (58) 242 2811
[redacted] Clinical Scientist	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted] Biostatistician	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted] Medical Safety Officer	Phone: +41 [redacted] E-mail: [redacted].pmi.com
[redacted] Clinical Study Manager	Phone: +41 [redacted] Mobile : +41 [redacted] E-mail: [redacted]@pmi.com

[redacted] Clinical Study Manager	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com

13.1.3 Other Responsibilities

Any SAEs or pregnancies will be handled by:

[redacted]

Fax: +41 [redacted]
E-mail: [redacted].com

Details of the laboratories conducting the clinical safety laboratory services and biopharmaceutical analyses are shown in Appendix B.

13.2 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the subject. An agreement to disclose any such information will be obtained from the subject in writing and signed by the subject, in compliance with all local and national data protection and privacy legislation.

The name of the subjects participating in this study will be kept confidential. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their subject (or randomization) number/code, sex and age, but not by name, initial, or any other details relating to identifiable person (*e.g.*, address, social security number, medical chart number, etc.). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

The blood samples for transcriptomics and lipidomics, and the data related to these samples will be anonymized. Anonymized data and samples are initially single or double coded where the link between the subjects' identifiers and the unique code(s) is subsequently deleted. This is applicable for the blood bio-banking for transcriptomics and lipidomics only.

Any documents that allow full identification of the subject (e.g., the subject's signed ICF) must be maintained in confidence by the Investigator. If any document relating to this study shows a subject's name or any other details relating to an identifiable person (*e.g.*, address, social security number, medical chart number, etc.), the name or other identifiable details must be

obscured before a copy of that document is supplied to the Sponsor or the Sponsor's authorized representative.

13.3 Access to Source Documentation

Subjects will be informed that, during the course of the clinical study, the Sponsor, any authorized representatives of the Sponsor, IRB/IEC or regulatory authorities may inspect their medical records to verify the information collected and ensure that all personal information made available for inspection is handled in the strictest confidence and in accordance with national and local data protection and privacy legislation.

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

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study and the actions taken will be maintained by the Investigator/study site for the study, as required by ICH/GCP and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in section 8 of the ICH Tripartite Guideline for Good Clinical Practice [1].

Essential documents must be retained by the Investigator for a minimum of:

- At least 15 years after completion or discontinuation of the study.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Signed informed consent documents for all subjects and master ICF.
- Subject identification code list, Screening log and Enrollment log (if applicable).
- Record of all communications between the Investigator and the IRB/IEC, composition of the IRB/IEC.
- Record of all communications/contact between the Investigator, the Sponsor, and its authorized representatives.

- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curricula vitae, and their signatures.
- Investigator logs.
- CRFs, study specific questionnaires (and associated data/scoring).
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (e.g., ECGs, consultation reports, physical examination, laboratory records) or any electronically captured study source data.
- Clinical laboratory reports, laboratory normal ranges.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).
- Record of any body fluids or tissue samples collected and retained.
- Information regarding subjects' discontinuation and any follow-up.

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

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

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

The Investigator or designee must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If an Investigator or designee is unable to meet this obligation, they must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study for 15 years after the CSR has been finalized.

13.5 Clinical Study Report

The Sponsor must ensure that a CSR for this study is prepared regardless of whether the study is completed or prematurely terminated.

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

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

The results of the additional variables will be presented in the study CSR.

13.6 Financial Disclosure

Investigators and designees are required to provide financial disclosure information to the Sponsor. In addition, the Investigators and designees must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IRB/IEC, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice will be given to the Sponsor prior to any such disclosure.

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

13.8 Insurance

The Sponsor is responsible for AEs and health damage of the subjects that are associated with the CHTP 1.0 product or with study procedures which are used during the study, except for AEs and health damage of the subjects caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Investigator or the clinical study site or the subjects. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

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APPENDIX A SCHEDULE OF EVENTS

Table A1 Study Assessments (Separate Table [Table A2] Shown for 24-hour Urine Collections)

	Screening	Confinement Period									Safety Follow-Up
Study Day	**Day -45 to Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6 (Day of Discharge)**	**Day 6 to Day 13**
One informed consent for study participation/ICF for bio-banking	•										
Two informed consent forms for long-term bio-banking	•										
Admission/discharge		•								•	
Advice on the risk of smoking/smoking cessation advice/debrief	•	•								•	
Inclusion/exclusion criteria	•	•									
Enrolment		•									
Randomization				•							
Demographics, medical history, concomitant diseases	•										
Vital signs [a]	•	•	•	•	•	•	•	•	•	•	
Physical examination [b]	•	•								•	
Spirometry [c]	•			•						•	
Prior/concomitant medication	•	•	•	•	•	•	•	•	•	•	
B/U: Hematology, clinical chemistry, urine analysis	•			•						•	

	Screening	Confinement Period									Safety Follow-Up
Study Day	**Day -45 to Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6 (Day of Discharge)**	**Day 6 to Day 13**
Electrocardiogram	•									•	
Chest X-ray [d]	•										
B: HIV, hepatitis B and C	•										
U: Urine drug screening, urine cotinine screening test	•	•									
U: Pregnancy test	•	•								•	
Alcohol breath test	•	•									
FTND	•										
Identification of the current cigarette brand	•	•									
Questions about smoking history/habits and intention to quit smoking	•	•									
CHTP 1.0 demonstration	•										
CHTP 1.0 product test [e]		•									
CO breath test [f]			•	•	•	•	•	•	•		
B: BoExp in blood: COHb [g]			•	•	•	•	•	•	•		
B: BoExp in plasma: nicotine, cotinine [h]			•	•	•	•	•	•	•		
B: CYP1A2 activity				•					•		
B: CYP2A6 activity [c]				•						•	
QSU-brief questionnaire [i]			•	•	•	•	•	•	•		

	Screening	Confinement Period									Safety Follow-Up
Study Day	**Day -45 to Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6 (Day of Discharge)**	**Day 6 to Day 13**
MNWS (revised version) [k]				•	•	•	•	•	•	•	
MCEQ (modified version; CHTP 1.0 and CC arms) [k]			•	•	•	•	•	•	•		
Assessment of cough				•	•	•	•	•	•	•	
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•
Collection of CC butts for accountability		•	•	•	•	•	•	•	•		
Collection of used CHTP 1.0 sticks for accountability		•			•	•	•	•	•		
Collection of used CHTP 1.0 sticks for plug and diffuser analysis								•			
HPT questionnaire (CHTP 1.0 and CC arms) [l]			•		•			•			
HPT			•		•			•			
B: Bio-banking [m]				•						•	

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

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

b. Physical examination and height (only at Screening), body weight and calculated BMI.

c. At Screening, spirometry needs to be done prior at least 1 hour after having stopped smoking. On Day -1 and Day 6, spirometry, and CYP2A6 blood sampling has to be done prior to smoking.

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

e. On Day -3, CHTP 1.0 product test to be conducted after enrolment. After the product test, subjects not ready to use the CHTP 1.0 for 5 days will be discontinued.

f. CO breath test; Day -2 to Day 5: the test will be conducted once per day, preferably in the evening around 08:00 PM ± 1hour in conjunction with COHb tests, where applicable.

g. COHb; Assessments should be done in conjunction with CO breath tests, where applicable. Day -2 to Day 5: one blood sample in the evening around 08:00 PM ± 1 hour.

h. Nicotine/cotinine; Day -2 to Day 5 (both CHTP 1.0 and CC arms): one blood sample around 08:00 ± 1 hour.

i. QSU-brief: daily, from Day -2 to Day 5.

j. MNWS daily from Day -1 to Day 6.

k. MCEQ: daily from Day -2 to Day 5.

l. On Day -2, HPT and HPT questionnaire will be done in all subjects using CC compatible with the HPT SODIM® device. On Day 1 of the confinement period, HPT and HPT questionnaire will be done for every product use in all subjects in the CHTP 1.0 and CC arms. On Day 4 of the confinement period, HPT and HPT questionnaire will be done in all subjects using CC compatible with the HPT SODIM® device. Puffing topography with the HPT SODIM® device will not be done in subjects using CC that are incompatible with the HPT SODIM® device (e.g., slim CC).

m. Blood/plasma samples for further transcriptomics and lipidomics analyses will only be taken if additional consent for bio-banking is given by the subject.

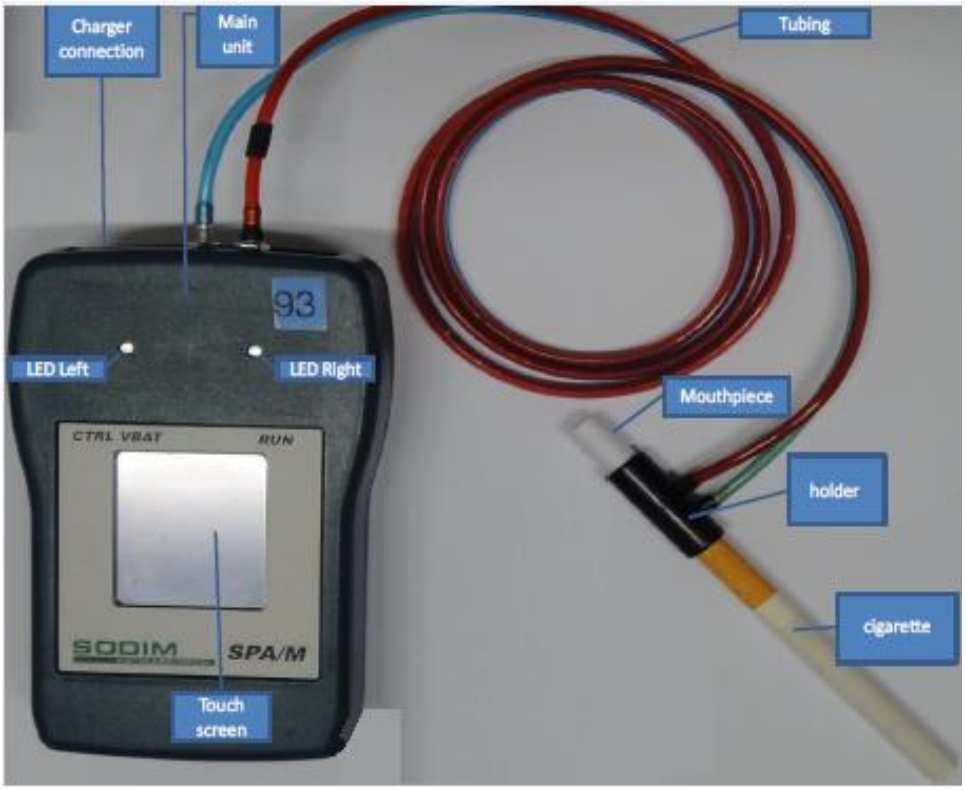
Table A2 Schedule for 24-hour Urine Collection Assessments

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

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

APPENDIX B PARTICIPATING LABORATORIES

APPENDIX C HPT SODIM® DEVICE



APPENDIX D SUMMARY OF BIOMARKERS OF EXPOSURE TO HPHC

HPHC [smoke phase]	HPHC List	Biomarker	Matrix	$t_{1/2}$	Reduced List of BoExp
1,3-Butadiene [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	Monohydroxybutenylmercapturic acid (MHBMA)	Urine	4 to 16 h	●
1-Aminonaphthalene [particulate]	FDA-18, FDA-93, HC PMI-58	1-Aminonaphthalene (1-NA)	Urine	Not described	
2-Aminonaphthalene [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	2-Aminonaphthalene (2-NA)	Urine	9 h	
4-Aminobiphenyl [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	4-Aminobiphenyl (4-ABP)	Urine	26 h	
Acrolein [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	3-Hydroxypropyl-mercapturic acid (3-HPMA)	Urine	10 h	●
Acrylonitrile [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	2-Cyanoethylmercapturic acid (CEMA)	Urine	17 h	●
Benzene [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	S-Phenylmercapturic acid (S-PMA)	Urine	9 to 15 h	
Benzo[a]pyrene [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	3-Hydroxybenzo[a]pyrene B[a]P	Urine	3 to 4 h	●
Carbon monoxide [gas]	FDA-18 FDA-93 HC PMI-58 WHO-18	CO	Breath	/	●
Pyrene	FDA-18 FDA-93 HC PMI-58 WHO-18	Total 1-hydroxypyene (total 1-OHP)	Urine	6 to 35 h	●
Crotonaldehyde [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	3-Hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA)	Urine	2 days	

HPHC [smoke phase]	HPHC List	Biomarker	Matrix	$t_{1/2}$	Reduced List of BoExp
Ethylene oxide [gas]	FDA-93, PMI-58	2-Hydroxyethyl-mercapturic acid (HEMA)	Urine	5 h	
NNN [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	Total N-nitrosonornicotine (Total NNN)	Urine	15 h	●
o-Toluidine [gas]	FDA-93, PMI-58	o-Toluidine (o-TOL)	Urine	10 to 16 h	
Nicotine [particulate]	FDA-18, FDA-93, HC PMI-58	Nicotine (NIC-P)	Plasma	1 to 2 h	●
		Cotinine (COT-P) 3-OH Cotinine (3-OHCOTP)	Plasma	16 to 18 h -	●
		Nicotine equivalents (Neq)	Urine	16 h (estimated)	●

APPENDIX E ABNORMAL LABORATORY VALUES

ABNORMAL LABORATORY VALUES RATING: SERUM CHEMISTRY PARAMETERS

Serum Chemistry *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Sodium – Hyponatremia [25] (mmol/L)	< LLN - 130	-	< 130 - 120	< 120
Sodium – Hypernatremia [25] (mmol/L)	> ULN - 150	> 150 - 155	> 155 – 160 hospitalization indicated	> 160
Potassium – Hyperkalemia [25] (mmol/L)	> ULN - 5.5	> 5.5 - 6.0	> 6.0 - 7.0 hospitalization indicated	> 7.0
Potassium – Hypokalemia [25] (mmol/L)	< LLN - 3.0	< LLN - 3.0; symptomatic; intervention indicated	< 3.0 - 2.5 hospitalization indicated	< 2.5
Glucose – Hypoglycemia [25] (mg/dL) (mmol/L)	< LLN – 55 < LLN – 3.0	< 55 – 40 < 3.0 – 2.2	< 40 – 30 < 2.2 – 1.7	< 30; < 1.7
Glucose – Hyperglycemia [25] Fasting (mg/dL) (mmol/L)	> ULN - 160 > ULN - 8.9	> 160 - 250 > 8.9 - 13.9	> 250 - 500 > 13.9 - 27.8 hospitalization indicated	> 500 > 27.8
Creatinine increased [25]	> 1 – 1.5 x Baseline > ULN – 1.5 x ULN	> 1.5 – 3.0 x Baseline > 1.5 – 3.0 x ULN	> 3.0 x Baseline > 3.0 – 6.0 x ULN	> 6.0 x ULN
Albumin - Hypoalbuminemia [25] (g/dL) (g/L)	< LLN – 3 < LLN - 30	< 3 – 2 < 30 - 20	< 2 < 20	- -
Alkaline phosphatase increased [25]	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT/AST increased [25]	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN

Serum Chemistry *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Gamma-glutamyl transferase (GGT) increased [25]	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Blood bilirubin increased [25] (total and direct)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Cholesterol high [25]				
(mg/dL)	> ULN - 300	> 300 - 400	> 400 - 500	> 500
(mmol/L)	> ULN - 7.75	> 7.75-10.34	> 10.34-12.92	> 12.92
Triglycerides – Hypertriglyceridemia [25]				
(mg/dL)	150 – 300	> 300 – 500	> 500 – 1000	> 1000
(mmol/L)	1.71 – 3.42	> 3.42 – 5.70	> 5.70 – 11.40	> 11.4

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; GGT = Gamma-glutamyl transferase; LLN = Lower limit of the normal range; ULN = Upper limit of the normal range.

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

ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Anemia (hemoglobin) (g/dL) (mmol) g/L	 < LLN-10.0 < LLN-6.2 < 100	 < 10-8.0 < 6.2-4.9 < 100-80	< 8.0 < 4.9 < 80 Transfusion indicated	Life threateming consequences; urgent intervention indicated
Hemoglobin increase [25] (g/dL)	Increase in > 0 – 2 above ULN or above Baseline if Baseline is above ULN	Increase in > 2 – 4 above ULN or above Baseline if Baseline is above ULN	Increase in > 4 above ULN or above Baseline if Baseline is above ULN	-
WBC decrease [25] (cell/mm^3) 10^{-9}/l	 < LLN – 3000 < LLN – 3.0	 < 3000 – 2000 < 3.0 – 2.0	 < 2000 - 1000 < 2.0 – 1.0	 < 1000 < 1.0
Lymphocytes increase [25] (cell/mm^3)	 -	 > 4,000 – 20,000	 > 20,000	 -
Lymphocytes decrease [25] (cell/mm^3) 10^{-9}/l	 < LLN – 800 < LLN – 0.8	 < 800 - 500 < 0.8 – 0.5	 < 500 - 200 < 0.5 – 0.2	 < 200 < 0.2
Neutrophils decrease [25] (cell/mm^3) 10^{-9}/l	 < LLN – 1500 < LLN – 1.5	 < 1500 - 1000 < 1.5 – 1.0	 < 1000 - 500 < 1.0 – 0.5	 < 500 < 0.5
Platelets decrease [25] (cell/mm^3) 10^{-9}/l	 < LLN – 75,000 < LLN – 75.0	 < 75,000 – 50,000 < 75.0 – 50.0	 < 50,000 – 25,000 < 50.0 – 25.0	 < 25,000 < 25.0

Abbreviations: LLN = Lower limit of the normal range; ULN = Upper limit of the normal range; WBC = White blood cell.

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

ABNORMAL LABORATORY VALUES RATING: URINALYSIS PARAMETERS

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Protein [25]	1+ proteinuria; urinary protein < 1.0 g/24 hours	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hours	Urinary protein ≥ 3.5 g/24 hours	-

Abbreviations: ADL = Activities of daily living; IV = Intravenous.

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