PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

P2R-REXA-07-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 1.2 (CHTP 1.2), compared to continuing to use combustible cigarettes, for 5 days in confinement followed by 85 days in an ambulatory setting.
Short Title	Reduced exposure study using the CHTP 1.2 with 5 days in a confinement setting followed by 85 days in an ambulatory setting.
EUDRACT Number:	Not applicable
Product Name:	Carbon Heated Tobacco Product 1.2 (CHTP 1.2)
Study Number	P2R-REXA-07-EU
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version Number:	FINAL VERSION 5.0
Revision Date:	05 December 2016
Authors:	[redacted], Lead Clinical Scientist [redacted], Clinical Scientist [redacted], Biostatistician [redacted] Medical Safety Officer

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Summary of Changes

Clinical Study Protocol

P2R-REXA-07-EU

	Version	Date	Amendment
Current protocol	Final Version 5.0	05 December 2016	N°2
First amended protocol	Final Version 4.0	13 June 2016	N°1
Second updated protocol	Final Version 3.0	07 December 2015	Non-substantial amendment
First updated protocol	Final Version 2.0	02 November 2015	Non-substantial amendment
Original protocol	Final Version 1.0	22 October 2015	

INTRODUCTION

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

- the substantial and administrative changes between the first amended protocol P2R-REXA-07-EU (Final Version 4.0) dated 13 June 2016 and the current protocol version (Final Version 5.0) dated 05 December 2016 which is to be referred to Amendment N°2.

- the substantial and administrative changes between the second updated protocol P2R-REXA-07-EU (Final Version 3.0) dated 07 December 2015 and the first amended protocol (Final Version 4.0) dated 13 June 2016 which is to be referred to Amendment N^0 1.

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- the administrative changes between the first updated clinical study protocol P2R-REXA-07-EU (Final Version 2.0) dated 02 November 2015 and the second updated protocol (Final Version 3.0) dated 07 December 2015.

- the correction of the name of the investigational products in a few tables between the first updated clinical study protocol P2R-REXA-07-EU (Final Version 2.0) dated 02 November 2015 and the second updated protocol (Final Version 3.0) dated 07 December 2015.

- the main changes between the clinical study protocol P2R-REXA-07-EU (Final Version 1.0) dated 22 October 2015 and its updated version (Final Version 2.0) dated 02 November 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 4.0 to Final 5.0		
The current version (Final Version 5.0) dated 05 December 2016 is to be referred to Amendment N° 2		
From Final 3.0 to Final 4.0		
The first amended protocol version (Final Version 4.0) dated 13 June 2016 is to be referred to Amendment N° 1		
From Final 2.0 to Final 3.0		
	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], MD.
13.1.2	**Sponsor**	***Amended text:***

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		[redacted] Medical Safety Officer Phone: +41 [redacted] **Mobile: +41** [redacted] E-mail: [redacted]**@pmi.com** ***Old text:*** [redacted] Medical Safety Officer Phone: +41 [redacted] E-mail: [redacted]~~.pmi.com~~ ***Reason to change:*** The phone number and the e-mail address of the Sponsor's MSO have been accordingly adapted to the change of the MSO.
Synopsis	**Sample Size;: Title of Table 1**	***Amended text:*** Expected Mean Ratios and Coefficients of Variation for **CHTP 1.2/CC** after 5 Days or 90 Days of exposure ***Old text:*** *Expected Mean Ratios and Coefficients of Variation for ~~THS 2.2 Menthol/m~~CC after 5 Days or 90 Days of exposure* ***Reason to change:*** Correction of the names of the respective investigational products.
12.2	**Determination of Sample Size and Power Consideration; Title of Table 20; Title of Table 21**	***Amended text:*** Table 20: Expected Mean Ratios and Coefficients of Variation for **CHTP 1.2/CC** after 5 Days of exposure Table 21*:* Expected Mean Ratios and Coefficients of Variation for **CHTP 1.2/CC** after 90 Days of exposure ***Old text:***

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		Table 20: Expected Mean Ratios and Coefficients of Variation for ~~THS 2.2 Menthol/m~~CC after 5 Days of exposure *Table 21: Expected Mean Ratios and Coefficients of Variation for ~~THS 2.2 Menthol/m~~CC after 90 Days of exposure* ***Reason to change:*** Correction of the names of the respective investigational products.
From Final 1.0 to Final 2.0		
7.6.1	**Blood Samples**	***Amended text:*** "The maximal total volume of blood drawn for each subject will be around **303** mL, …, about **36** mL for long-term storage of the bio-banking samples of biomarkers, clinical risk endpoints and other circulating proteins (…), and **about 57** mL for long-term storage bio-banking samples for transcriptomics, lipidomics and DNA methylation sequencing analyses (only if additional consent is given)…". ***Old text:*** *"The maximal total volume of blood drawn for each subject will be around ~~452~~ mL, …, about ~~114~~ mL for long-term storage of the bio-banking samples of biomarkers, clinical risk endpoints and other circulating proteins (…) and ~~60~~ mL for long-term storage bio-banking samples for transcriptomics, lipidomics and DNA methylation sequencing analyses (only if additional consent is given)…".* ***Reason to change:*** To correct blood volumes to be drawn which were overcalculated.
7.6.3	**Bio-Banking for Long-Term Storage of Blood and Urine**	***Amended text:*** This is to obtain and store 2 x 1 mL of serum, 2 x 1 mL of **plasma** and 2 x 1 mL whole blood. ***Old text:*** *This is to obtain and store 2 x 1 mL of serum, 2 x 1 mL of ~~serum~~ and 2 x 1 mL whole blood.* ***Reason to change:*** To correct an error in writing.

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		Amended text: "…and serum/plasma/whole blood (**approx.** 36 mL of blood in total) will be collected as follows:" . ***Old text:*** *"…and serum/plasma/whole blood (36 mL of blood in total) will be collected as follows:".* ***Amended text:*** Serum/whole blood will be collected on Day -1, Day 6 and Visit 4, respectively (**approx.** 36 mL of blood in total with **approx.** 12 mL of blood draw per time point. ***Old text:*** *Serum/whole blood will be collected on Day -1, Day 6 and Visit 4, respectively (36 mL of blood in total with 12 mL of blood draw per time point.* ***Amended text:*** "… and whole blood for DNA methylation sequencing **approx. 57** mL of blood will **additionally** be collected in total." ***Old text:*** *"… and whole blood for DNA methylation sequencing ~~an additional~~ ~~60~~ mL of blood will be collected in total."* ***Amended text:*** On Day 1, Day 6 and at Visit 4, **approx.** 15 mL blood in total will be collected for transcriptomics… ***Old text:*** *On Day 1, Day 6 and at Visit 4, 15 mL blood in total will be collected for transcriptomics…* ***Amended text:*** For lipidomics analyses, **approx.** 12 mL blood in total will be collected on Day -1,… ***Old text:*** *For lipidomics analyses, 12 mL blood in total will be collected on Day -1,…* ***Amended text:*** For DNA methylation sequencing, **approx.** 30 mL blood in total will be collected on Day -1,…

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		Old text: *For DNA methylation sequencing, 30 mL blood in total will be collected on Day -1,…* ***Reason to change:*** Slight deviations in amount of blood during blood drawings are taken into consideration.

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SYNOPSIS

Sponsor:

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

Name of Product:

Carbon Heated Tobacco Product 1.2 (CHTP 1.2)

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

Study Number:

P2R-REXA-07-EU, no acronym

Study Short Title:

Reduced exposure study using the CHTP 1.2 with 5 days in a confinement setting and 85 days in an ambulatory setting.

Primary Objectives and Endpoints:

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

   Endpoints (Day 5):

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

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

2. To demonstrate the reduction of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC for 90 days

   Endpoint (Visit 4):

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

Secondary Objectives and Endpoints:

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

   Endpoint (measured daily):

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

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

   Endpoints (Day 5 to Visit 4):

   - BoExp to HPHCs in urine (expressed as quantity excreted or concentration adjusted for creatinine in 24-hour urine):
     - MHBMA (Visit 4 only)
     - 3-HPMA (Visit 4 only)
     - S-PMA (Visit 4 only)
     - Total NNAL (Day 5 only)
     - BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene (Day 5, Visit 4)
     - BoExp to pyrene: total 1-hydroxypyrene (total 1-OHP) (Day 5, Visit 4)
     - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN) (Day 5, Visit 4)
     - BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP) (Day 5, Visit 4)
     - BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA) (Day 5, Visit 4)
     - BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA) (Day 5, Visit 4)

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- BoExp to o-toluidine: o-toluidine (o-tol) (Day 5, Visit 4)
- BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA) (Day 5, Visit 4)
- BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA) (Day 5, Visit 4)
- BoExp to crotonaldehyde: 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA) (Day 5, Visit 4)

- BoExp to CO:
  - CO in exhaled breath (expressed as ppm) (Day 5, Visit 4)
  - COHb in blood (expressed as % of saturation of hemoglobin) (Visit 4 only)

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

   Endpoints (Day 1 to Visit 4):

   - BoExp to CO:
     - CO in exhaled breath (expressed as ppm)
     - COHb in blood (expressed as % of saturation of hemoglobin)

   - BoExp to HPHCs in urine (expressed as quantity excreted and concentration adjusted for creatinine in 24-hour urine):
     - MHBMA
     - 3-HPMA
     - S-PMA
     - Total NNAL
     - Total 1-OHP
     - Total NNN
     - 4-ABP
     - 1-NA
     - 2-NA
     - o-tol
     - CEMA
     - HEMA
     - 3-hydroxybenzo(a)pyrene
     - HMPMA

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

   Endpoints (Day 1 to Visit 4):

   - Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide), expressed as concentration adjusted for creatinine in 24-hour urine
   - Nicotine and cotinine plasma concentrations

5. To determine the changes over the entire exposure period in lung functions in smokers switching from CC to the CHTP 1.2 as compared to those continuing to use CC

   Endpoint (Day 6 and Visit 4):

   - Spirometry (pre- and post-bronchodilator): forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow (FEF 25-75)

   Endpoint (Day 1 to Visit 4):

   - Cough assessment by Visual Analog Scale (VAS) and Likert Scales and one open question

6. To monitor selected cardiovascular clinical risk endpoints over the entire exposure period in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC

   Endpoints (Day 6 to Visit 4):

   - Systolic and diastolic blood pressure on Day 6, at Visit 2, Visit 3, and Visit 4
   - High sensitive C-reactive protein (hs-CRP), blood glucose, myeloperoxidase (MPO), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) in serum at Visit 2, Visit 3, and Visit 4
   - Fibrinogen, homocysteine in plasma at Visit 2, Visit 3, and Visit 4
   - Hemoglobin A1c (HbA1c) in blood at Visit 4
   - Apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) in serum at Visit 4
   - Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6, at Visit 2, Visit 3, and Visit 4
   - White blood cell (WBC) and platelet counts in blood on Day 6, at Visit 2, Visit 3, and Visit 4

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- 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5, at Visit 2, Visit 3, and Visit 4 (expressed as concentration adjusted for creatinine)
- Body weight and waist circumference at Visit 4

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

   Endpoints (Day 5 to Visit 4):

   - Epi-prostaglandin F2α (8-epi-PGF2α) in 24-hour urine on Day 5, at Visit 2, Visit 3, and Visit 4 (expressed as concentration adjusted for creatinine)
   - Ratio of 8-epi-prostaglandin F2α (8-epi-PGF2α) to prostaglandin F2α (PGF2α) in plasma on Day 5 and at Visit 4
   - 8-Hydroxy-2'-deoxyguanosine (8-OHdG) in 24-hour urine on Day 5, at Visit 2, Visit 3, and Visit 4 (expressed as concentration adjusted for creatinine)
   - 4-Hydroxy-2-nonenal (4-HNE) in serum on Day 5 and at Visit 4 [a]
   - Total anti-oxidant capacity (TAC) in serum on Day 5 and at Visit 4

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

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

   Endpoint (Day 5 and Visit 4):

   - Molar metabolic ratio of paraxanthine/caffeine in plasma

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

   Endpoints:

   - Adverse events (AEs) / serious adverse events (SAEs) and incidence of CHTP 1.2 malfunctions and misuse, [redacted]
   - Vital signs
   - Electrocardiogram (ECG)
   - Clinical chemistry, hematology, and urine analysis safety panel
   - Physical examination
   - Concomitant medications

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Exploratory Objectives and Endpoints:

1. To describe the following parameters in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC
   - Excretion of mutagenic material in 24-hour urine: Ames mutagenicity test (YG1024+S9): Day 5 and Visit 4.
   - Subjective effects of smoking:
     - Questionnaire of Smoking Urges (QSU), (brief version): Day 1 to Visit 4
     - Fagerström Test for Nicotine Dependence (FTND), (revised version): Visit 4
     - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ): Day 1 to Visit 4
   - Cytochrome P450 2A6 (CYP2A6) enzymatic activity:
     - the molar metabolic ratio of *trans*-3'-hydroxycotinine/cotinine: Day 6 and Visit 4
   - Intent to Use of CHTP 1.2:
     - Intent to Use of CHTP 1.2 Questionnaire (ITUQ): only in smokers switching from CC to CHTP 1.2: Day 6 and Visit 4

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

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

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

   Endpoint (Visit 4):
   - Prochaska "Stage of Change" Questionnaire

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

   Endpoints:

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

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

Study Hypothesis:

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

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 after 5 days of exposure, and in total NNAL after 90 days of exposure in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability.

Study Design

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

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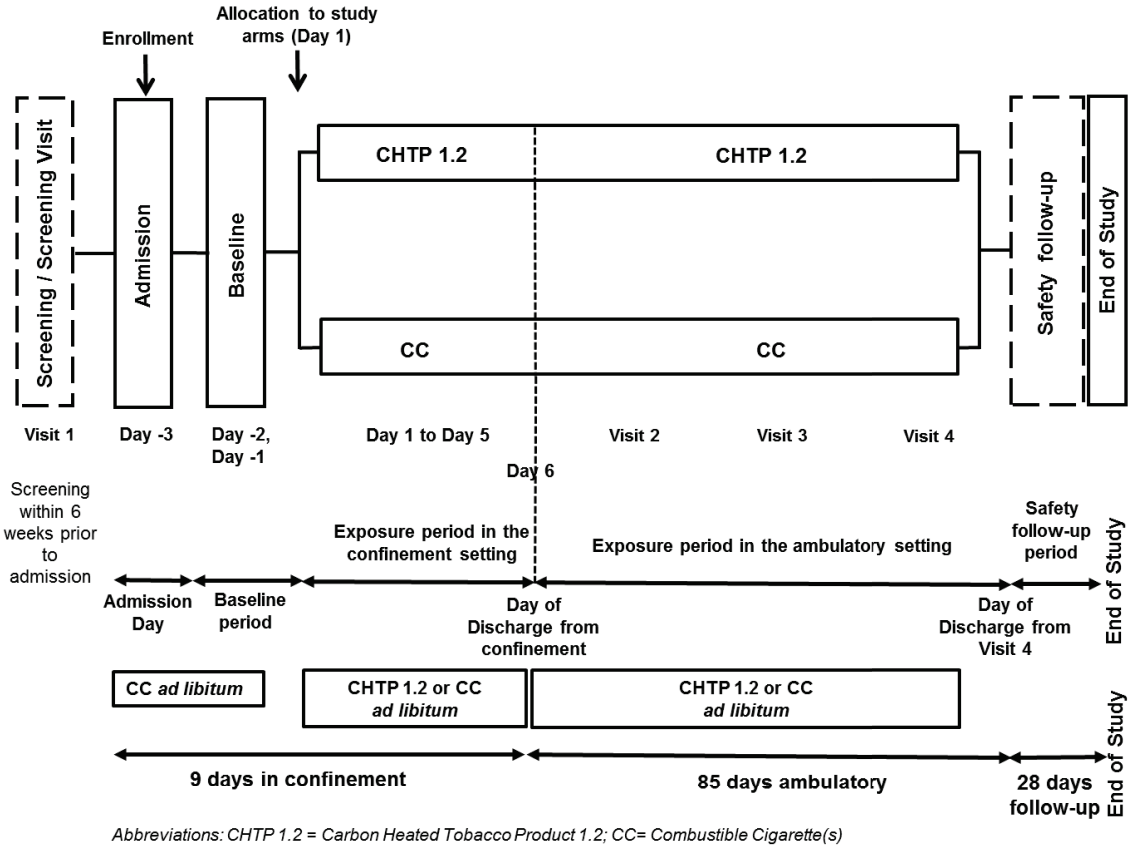

Figure 1 Study Design

- <u>The Screening Period (from Day -45 until Admission on Day -3):</u>

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

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

  Subjects will be in a confinement setting for 9 days from Day -3 onwards.

  On Day -3 (Admission), after all inclusion/exclusion criteria are checked, all eligible subjects will be enrolled and perform a product test using up to 5 CHTPs 1.2. However, before smoking and the product testing, the sample for CYP2A6 activity has to be taken. After the product test, subjects not willing and ready to use the CHTP 1.2 will be

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discontinued. After the sample for CYP2A6 activity has been taken, and the product test has been performed, smokers will be allowed to smoke their single preferred brand of CC *ad libitum* until 11.00 PM. Use of any tobacco/nicotine containing product other than CC and CHTP 1.2 for the product test will not be allowed after Admission.

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

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

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

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

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

- The Exposure Period (from Day 1, 06:30 AM until Discharge at Visit 4):

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

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

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

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

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

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

Subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days.

- The Exposure Period in the Ambulatory Setting (from Discharge on Day 6 until Discharge at Visit 4):

  Subjects will be required to make three visits (Visit 2, Visit 3, and Visit 4) to the investigational site. Each visit will cover 2 consecutive days on site. For Visit 2 and Visit 3, the subject will check-in in the morning on the first day of the respective visit and will check-out on the second day of the visit. For Visit 4, the subject will check-in in the morning on the first day of the visit, and will be discharged on the second day of the visit after having performed all the safety examination procedures.

  Twenty four-hour urine will be collected at each visit (Visit 2, Visit 3, and Visit 4) at the site. The collection of 24-hour urine will start on the first day of the respective visits and will end 24 hours later on the following day. On the first day of Visit 2, Visit 3, and Visit 4, subjects in the CHTP 1.2 and CC arms will be allowed to use their assigned product from the time of check-in until 11:00 PM. On the second day of Visit 2 and Visit 3, product use will be allowed from 06:30 AM onwards. The exposure period to the assigned IP will end at 11:00 PM on the first day of Visit 4.

  On the second day of Visit 4 (Day 91), subjects who wish to smoke CC or use other nicotine/tobacco-containing products will be allowed to do so, but only after the end of 24-hour urine collection and after spirometry and sampling for CYP2A6 activity have been performed.

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

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

During the confinement and ambulatory settings:

- Any subject, who wants to attempt to quit using any tobacco products during the study (e.g., CHTP 1.2 and CC) will be encouraged to do so and will be referred to

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appropriate medical services. This will not affect subject's financial compensation, and the subject will remain in the study.

- The Safety Follow-up Period (from Discharge at Visit 4 until the End of the Safety Follow-up Period):

  After Discharge at Visit 4 or the date of early termination, subject will enter a 28-day Safety Follow-up Period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the study. At the end of the Safety Follow-up Period, all ongoing AEs will be documented as "ongoing" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner for follow-up on ongoing AEs.

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

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

  The individual end of study (EOS) date for a subject is defined as either the Discharge at Visit 4 or the date of early termination followed by the 28-day Safety Follow-up Period.

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

Study Population and Main Criteria for Inclusion/Exclusion:

Approximately 120 smoking, healthy Caucasian female or male adult subjects meeting the following main inclusion criteria:

- Subject is at least 28 years old
- Subject is Caucasian
- Subject is healthy, as judged by the Investigator
- Subject has smoked on average at least 10 commercially available non-menthol CCs per day (no brand restrictions) at least for the last 6 weeks prior to the Screening Visit and Admission, respectively, based on self-reporting
- Subject has smoked at least for the last 10 years
- Subject does not plan to quit smoking in the next 6 months
- Subject is ready to comply with the study procedures (e.g., to use CHTP 1.2 for the duration of the study)

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

Investigational Products; Dose; and Mode of Administration:

- Carbon Heated Tobacco Product 1.2 (CHTP 1.2). CHTP 1.2 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 128 to 169 days, including a Screening Period of up to 42 days prior to Admission on Day -3, a 9-day confinement setting (Day -3 to Discharge on Day 6) followed by a 85-day ambulatory setting (from the Discharge on Day 6 to the Discharge at Visit 4), and a 28-day Safety Follow-up Period. The EOS of the entire study is the last individual EOS time point during the study.

Statistical Methods:

Analysis of BoExp will be conducted on the natural log scale. The Day 5- or Visit 4-BoExp levels 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 6 weeks prior to Admission (value at Admission for stratification), and Baseline value of the BoExp. Relative effects will be provided. 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 conducted using a one-sided test with 2.5% type I error probability, and all quoted confidence intervals (CIs) will be two-sided 95% CIs.

Sample Size:

The analysis set to analyze the primary endpoints will be the Per-Protocol (PP) population. It is assumed that a minimal number of subjects will be excluded from the PP set in confinement for both arms and CC in ambulatory, whereas at least 50% will remain in the PP set in ambulatory for CHTP 1.2, therefore a 2:1 randomization ratio was chosen. Using the below assumptions, a total of 120 subjects (~80 in the CHTP 1.2 arm, and ~40 in the CC arm) will be randomized.).

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Table 1 Expected Mean Ratios and Coefficients of Variation for CHTP 1.2/CC after 5 Days or 90 Days of exposure

Timepoint of assessment	Primary endpoint	CHTP 1.2/CC MR (CV)
Day 5	COHb	0.40 (0.32)
Day 5	3-HPMA	0.30 (0.50)
Day 5	MHBMA	0.15 (0.70)
Day 5	S-PMA	0.20 (0.70)
Day 90	Total NNAL	0.30 (0.60)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = Combustible cigarettes; COHb = Carboxyhemoglobin; CV = Coefficients of variation; MHBMA = Monohydroxybutenyl mercapyuric acid; MR = Mean ratios; S-PMA = S-phenylmercapturic acid; Total NNAL = Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CHTP 1.2 = Carbon Heated Tobacco Product 1.2.

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

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LIST OF IN-TEXT FIGURES

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LIST OF APPENDICES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

1-NA	1-aminonaphthalene
2-NA	2-aminonaphthalene
3-HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
4-HNE	4-hydroxy-2-nonenal
8-epi-PGF2α	8-epi-prostaglandin F2α
8-OHdG	8-hydroxy-2'-deoxyguanosine
11-DTX-B2	11-dehydro-thromboxane B2
ADL	Activities of daily living
AE	Adverse event
ANOVA	Analysis of variance
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ATS	American Thoracic Society
BMI	Body mass index
BoExp	Biomarker of exposure
CAF	Caffeine
CC	Combustible cigarette(s)
CD	Compact disc
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
CHTP	Carbon Heated Tobacco Product
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
CRF	Case report form

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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
CVD	Cardiovascular diseases
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ENDs	Electronic nicotine devices
EOS	End of study
ERS	European Respiratory Society
FAS	Full analysis set
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström Test for Nicotine Dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HEMA	2-hydroxyethylmercapturic acid
HIV	Human immunodeficiency virus
HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
HPHCs	Harmful and potentially harmful constituents

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hs-CRP	High sensitive C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	International Ethic Committee
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITUQ	Intent to Use Questionnaire
IU	International unit
IV	Intravenous
IxRS	Interactive web/voice response system
LDL	Low density lipoprotein
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
LPO	Lipid peroxidation
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenylmercapturic acid
MPO	Myeloperoxidase
MR	Mean ratio
MRTP	Modified risk tobacco product
n	Number of subjects
NEQ	Nicotine equivalents: molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1butanone
NRT	Nicotine replacement therapy
NSAID	Nonsteroidal anti-inflammatory drugs
o-tol	o-toluidine

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PGF2α	Prostaglandin F2α
PGHSs	Prostaglandin-endoperoxide synthases
PI	Principal Investigator
PMI	Philip Morris International
PP	Per protocol
PUFAs	Polyunsaturated fatty acids
PX	Paraxanthine
QC	Quality control
QSU-brief	Questionnaire of Smoking Urges
ROS	Reactive oxygene species
RRP	Reduced risk products
S-PMA	S-phenylmercapturic acid
SA	Smoking abstinence
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Smoking cessation
SD	Standard deviation
SES	Socio-Econonomic Status Questionnaire
SHM	Sample handling manual
sICAM-1	Soluble inter-cellular adhesion molecule-1
SMF	Study master file
SMP	Safety management plan
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
TAC	Total anti-oxidant capacity
TC	Total cholesterol

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TG	Triglycerides
Total 1-OHP	Total 1-hydroxypyrene
Total NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
Total NNN	Total N-nitrosonornicotine
[redacted]	[redacted]
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual Analogue Scale
vWF	von-Willebrand factor
WBC	White blood cell (count)
WHO	World Health Organization

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Explanation of Terms

The following special terms are used in this protocol:

Combustible cigarette (CC)	The term "combustible cigarette" refers to commercially available cigarettes (manufactured) and excludes cigars, pipes, bidis, and other nicotine-containing products.
Carbon Heated Tobacco Product 1.2 (CHTP 1.2)	CHTP 1.2 is a non-menthol tobacco stick which is comparable in shape and form, and is used in a similar manner to a combustible cigarette except that the tobacco contained in the CHTP 1.2 is heated by a Carbon Heat Tip and not burned like in a combustible cigarette..
End of study (EOS)	The individual end of the study (EOS) for a subject is defined as either the Discharge at Visit 4 or the date of early termination followed by the 28-day Safety Follow-up Period. The EOS of the entire study is the last individual EOS time point during the study.
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.

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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. No assessment can be performed on the subjects 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.

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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 informed 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 personally signed and 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.

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- One separate ICF to obtain consent for serum/plasma and urine collection and long-term storage for subsequent analysis of biomarkers of exposure, clinical risk endpoints and other circulating proteins, 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.
- One separate ICF to obtain consent for collection and long-term storage of whole blood samples for further analysis of DNA methylation sequencing.

1.3.3 Informed Consent Form for Additional Research Related to the Bioanalytical Method for 8-epi-PGF2α and PGF2α Analysis

During the course of the study, the most recent development of the assay to measure the 8-epi-PGF2α to PGF2α ratio showed that the ratio is not an effective endpoint for the determination of oxidative stress (Celerion Laboratory, unpublished data) in contrast to what was published (see section 4.2). IRB was informed on the 2nd of June that blood samples dedicated to this analysis were no longer collected as from 1st of June for subjects who have not still completed the study.

However, blood samples collected up to June 1st will be analyzed for the purpose of the study, and the results will be included in the clinical study report as part of the main study.

All subjects will be informed and asked to sign and date a separate ICF to consent for use of the 8-iso-PGF2α/ PGF2α analysis performed on already collected samples for bioanalytical research purposes.The subject's participation in the study does not depend on his/her consent to this separate ICF.

1.3.4 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

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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.

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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 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, taste, ritual and sensory experience 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 90 of them have been categorized as HPHCs [6].

The product developed by PMI, and being assessed in this study, is the Carbon Heated Tobacco Product 1.2 (CHTP 1.2). With this product, the heating of the tobacco does not exceed a well-defined temperature profile during use, which ensures heating without combustion of the tobacco, and at the same time provides an acceptable consumer experience in a consistent manner.

CHTP 1.2 is a non-menthol tobacco stick which has similar appearance, and is used in a similar manner to a CC. To use CHTP 1.2, the consumer removes the protective cap and uses regular matches or lighter to ignite the carbon heat source, except that this process should be done while holding CHTP 1.2 in the hand, rather than in the mouth (like for a CC). After a short

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pause to allow the tobacco to become heated, the aerosol generated by the heating process is inhaled by placing the filter of CHTP 1.2 in the mouth (or on the lips) and drawing air through CHTP 1.2.

The non-clinical assessment of CHTP 1.2 described in the Investigator's Brochure supports the initiation of the clinical studies [7]. No new or increased toxicological hazard in the product's aerosol was detected compared with CC smoke.

The non-clinical assessment of CHTP 1.2 is described in the IB and supports the clinical assessment of CHTP 1.2 [7].

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 1.2. After 5 days of exposure marked reductions in exposure to HPHCs in the CHTP 0.1 arm and smoking abstinence (SA) arm compared to subjects continuing smoking CC were observed, and no safety concern was revealed. No clinical studies have been conducted with CHTP 1.2. One randomized, controlled, 2-period, 2-sequence, single-use crossover study with CHTP 1.1 M (Carbon Heated Tobacco Product 1.1 Menthol) is ongoing in Japan (ClinicalTrials.gov Identifier: NCT02466412) [8]. One randomized, controlled, open-label, 2-arm, parallel group, single-center study with CHTP 1.0 is currently ongoing in Poland (ClinicalTrials.gov Identifier: NCT02503254) [9].

2.2 Purpose of the Study

The overall goal of the study is to demonstrate reduction in the levels of BoExp to selected HPHCs and to obtain safety information in healthy subjects using the CHTP 1.2 as compared to smokers continuing smoking CC in a confinement setting for 5 days (exclusive use) followed by an ambulatory setting of 85 days.

Importantly, the study will provide information on biological and functional changes in clinical risk endpoints, in particular, endpoints on oxidative stress upon use of CHTP 1.2. Furthermore product evaluation, assessment of product use and subjective effects of smoking will be performed.

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 the Screening Visit, Admission, at Discharge on Day 6, and at Visits 2, 3 and 4. The advice will follow the recommendations of the World Health Organization (WHO) "Evidence based Recommendations on the Treatment of Tobacco Dependence" [10]. Subjects

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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)
- Using commonly accepted research and scientific standards (e.g., blood samples not to exceed blood donation standards)

All risks related to the IP will be explained in detail to the subjects.

Risk mitigation will include:

- 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 1.2 may lead to unforeseeable risk. Subjects will be informed that CHTP 1.2 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.

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3 STUDY OBJECTIVES

3.1 Primary Objectives and Endpoints

The primary objectives of this study are:

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

   Endpoints (Day 5):

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

2. To demonstrate the reduction of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC for 90 days

   Endpoint (Visit 4):

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

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

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

   Endpoint (measured daily):

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

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

   Endpoints (Day 5 to Visit 4):

   - BoExp to HPHCs in urine (expressed as quantity excreted or concentration adjusted for creatinine in 24-hour urine):
     - MHBMA (Visit 4 only)
     - 3-HPMA (Visit 4 only)
     - S-PMA (Visit 4 only)
     - Total NNAL (Day 5 only)
     - BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene (Day 5, Visit 4)
     - BoExp to pyrene: total 1-hydroxypyrene (total 1-OHP) (Day 5, Visit 4)
     - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN) (Day 5, Visit 4)
     - BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP) (Day 5, Visit 4)
     - BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA) (Day 5, Visit 4)
     - BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA) (Day 5, Visit 4)
     - BoExp to o-toluidine: o-toluidine (o-tol) (Day 5, Visit 4)
     - BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA) (Day 5, Visit 4)
     - BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA) (Day 5, Visit 4)
     - BoExp to crotonaldehyde: 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA) (Day 5, Visit 4)
   - BoExp to CO:
     - CO in exhaled breath (expressed as ppm) (Day 5, Visit 4)
     - COHb in blood (expressed as % of saturation of hemoglobin) (Visit 4 only)

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

   Endpoints (Day 1 to Visit 4):

   - BoExp to CO:

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  - CO in exhaled breath (expressed as ppm)
  - COHb in blood (expressed as % of saturation of hemoglobin)

- BoExp to HPHCs in urine (expressed as quantity excreted and concentration adjusted for creatinine in 24-hour urine):
  - MHBMA
  - 3-HPMA
  - S-PMA
  - Total NNAL
  - Total 1-OHP
  - Total NNN
  - 4-ABP
  - 1-NA
  - 2-NA
  - o-tol
  - CEMA
  - HEMA
  - 3-hydroxybenzo(a)pyrene
  - HMPMA

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

   Endpoints (Day 1 to Visit 4):

   - Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide), expressed as concentration adjusted for creatinine in 24-hour urine
   - Nicotine and cotinine plasma concentrations

5. To determine the changes over the entire exposure period in lung functions in smokers switching from CC to the CHTP 1.2 as compared to those continuing to use CC

   Endpoint (Day 6 and Visit 4):

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- Spirometry (pre- and post-bronchodilator): forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow (FEF 25-75)

Endpoint (Day 1 to Visit 4):

- Cough assessment by Visual Analog Scale (VAS) and Likert Scales and one open question

6. To monitor selected cardiovascular clinical risk endpoints over the entire exposure period in smokers switching from CC to CHTP 1.2 as compared to smokers continuing to use CC

   Endpoints (Day 6 to Visit 4):

   - Systolic and diastolic blood pressure on Day 6, at Visit 2, Visit 3, and Visit 4
   - High sensitive C-reactive protein (hs-CRP), blood glucose, myeloperoxidase (MPO), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) in serum at Visit 2, Visit 3, and Visit 4
   - Fibrinogen, homocysteine in plasma at Visit 2, Visit 3, and Visit 4
   - Hemoglobin A1c (HbA1c) in blood at Visit 4
   - Apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) in serum at Visit 4
   - Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6, at Visit 2, Visit 3, and Visit 4
   - White blood cell (WBC) and platelet counts in blood on Day 6, at Visit 2, Visit 3, and Visit 4
   - 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5, at Visit 2, Visit 3, and Visit 4 (expressed as concentration adjusted for creatinine)
   - Body weight and waist circumference at Visit 4

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

   Endpoints (Day 5 to Visit 4):

   - Epi-prostaglandin F2α (8-epi-PGF2α) in 24-hour urine on Day 5, at Visit 2, Visit 3, and Visit 4 (expressed as concentration adjusted for creatinine)
   - Ratio 8-epi-prostaglandin F2α (8-epi-PGF2α) to prostaglandin F2α (PGF2α) in plasma on Day 5 and at Visit 4

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- 8-Hydroxy-2'-deoxyguanosine (8-OHdG) in 24-hour urine on Day 5, at Visit 2, Visit 3, and Visit 4 (expressed as concentration adjusted for creatinine)
- 4-Hydroxy-2-nonenal (4-HNE) in serum on Day 5 and at Visit 4 [a]
- Total anti-oxidant capacity (TAC) in serum on Day 5 and at Visit 4

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

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

   Endpoint (Day 5 and Visit 4):

   - Molar metabolic ratio of paraxanthine/caffeine in plasma

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

   Endpoints:

   - Adverse events (AEs) / serious adverse events (SAEs) and incidence of CHTP 1.2 malfunctions and misuse, [redacted]
   - Vital signs
   - 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 1.2 as compared to smokers continuing to use CC
   - Excretion of mutagenic material in 24-hour urine: Ames mutagenicity test (YG1024+S9): Day 5 and Visit 4
   - Subjective effects of smoking:
     - Questionnaire of Smoking Urges (QSU), (brief version): Day 1 to Visit 4
     - Fagerström Test for Nicotine Dependence (FTND), (revised version): Visit 4

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- Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ): Day 1 to Visit 4

- Cytochrome P450 2A6 (CYP2A6) enzymatic activity: the molar metabolic ratio of *trans*-3'-hydroxycotinine/cotinine: Day 6 and Visit 4

- Intent to Use of CHTP 1.2:
  - Intent to Use of CHTP 1.2 Questionnaire (ITUQ): only in smokers switching from CC to CHTP 1.2: Day 6, and Visit 4

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

   Endpoint (daily):

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

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

   Endpoint (Visit 4):

   - Prochaska "Stage of Change" Questionnaire

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

   Endpoints:

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

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

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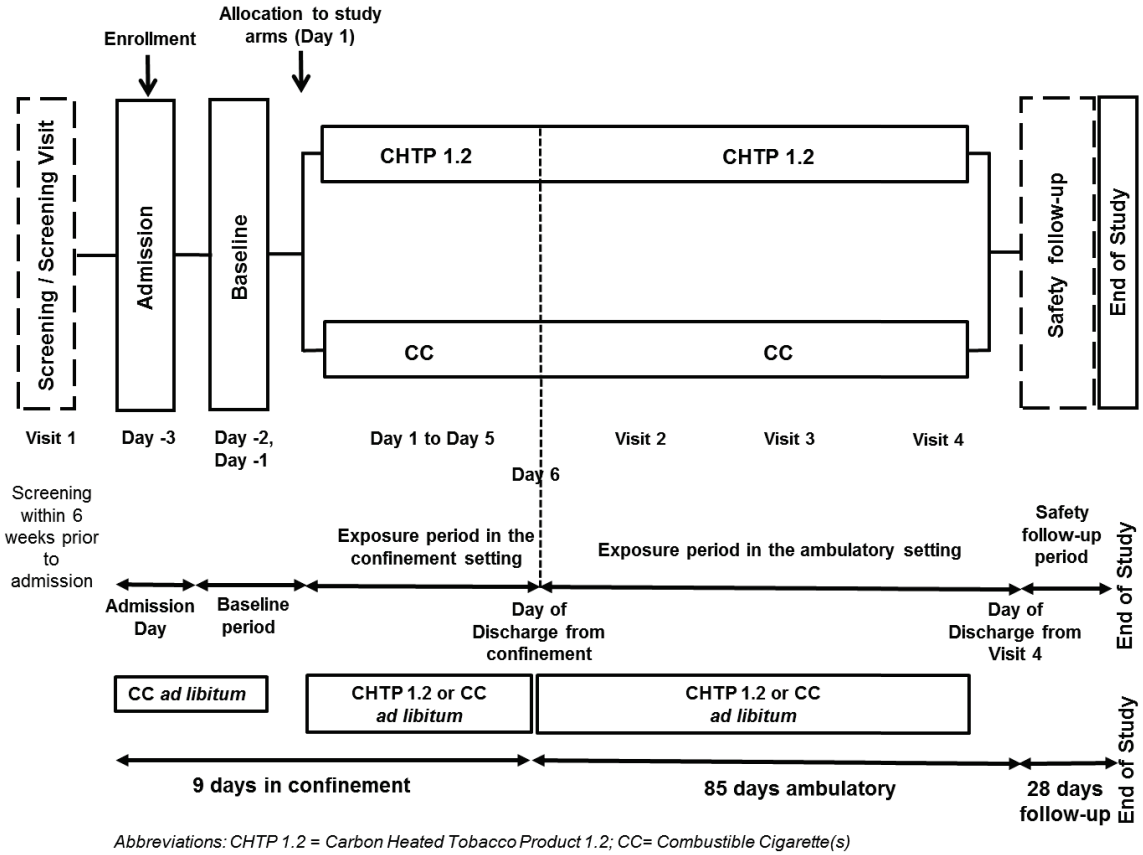
4 INVESTIGATIONAL PLAN

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 (smoking 10 to 19 CC/day vs. > 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 1.2 and CC in CHTP 1.2 and CC arms, respectively) will be ensured by strict distribution of each CHTP 1.2/CC on demand of the subject.



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

Figure 2 Study Design

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

  The Screening Period covers 6 weeks prior to Admission to the site. A demonstration of CHTP 1.2 (without product use) will be done by the site collaborators during the Screening Visit. At the Screening Visit, 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. At the end of the Screening Visit, subject will be instructed not to smoke in the morning prior to the admission to the site on the Admission Day.

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

  Subjects will be in a confinement setting for 9 days from Day -3 onwards.

  On Day -3 (Admission), after all inclusion/exclusion criteria are checked, all eligible subjects will be enrolled and then perform a product test using up 5 CHTPs 1.2. However, before smoking and the product testing, the sample for CYP2A6 activity has to be taken. After the product test, subjects not willing and ready to use the CHTP 1.2 will be discontinued. All subjects that are not enrolled are considered as screen failures. After the sample for CYP2A6 activity has been taken, and the product test has been performed, smokers will be allowed to smoke their single preferred brand of CC *ad libitum* until 11.00 PM. Use of any tobacco/nicotine containing product other than CC and CHTP 1.2 for the product test will not be allowed after Admission.

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

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

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

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

  Subjects will be informed about their randomized study arm by the study site staff on Day 1 prior to 06:30 AM. Subjects who do not complete the study after randomization will not be replaced.

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- The Exposure Period (from Day 1, 06:30 AM until Discharge at Visit 4):

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

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

    The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product (CHTP 1.2 or CC, exclusively) from 06:30 AM until around 11:00 PM each day. Subjects who are willing to attempt quitting using any tobacco products during the study will be encouraged to do so and will be referred to a smoking cessation aid service.

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

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

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

    Subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days.

  - The Exposure Period in the Ambulatory Setting (from Discharge on Day 6 until Discharge at Visit 4):

    At the end of the confinement period prior to Discharge on Day 6, subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days.

    Subjects will be required to make three visits (Visit 2, Visit 3 and Visit 4) to the investigational site. Each visit will cover 2 consecutive days on site. For Visit 2 and Visit 3, the subject will check-in in the morning on the first day of the respective visit and will check-out on the second day of the visit. For Visit 4, the subject will check-in in the morning on the first day of the visit, and will be discharged on the second day of the visit after having performed all the safety examination procedures.

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Twenty four-hour urine will be collected at each ambulatory visit (Visit 2, Visit 3, and Visit 4) at the site. The collection of 24-hour urine will start on the first day of the respective visits and will end 24 hours later on the following day. On the first day of Visit 2, Visit 3, and Visit 4, subjects in the CHTP 1.2 and CC arms will be allowed to use their assigned product from the time of check-in until 11:00 PM. On the second day of Visit 2 and Visit 3 product use will be allowed from 06:30 AM onwards. The exposure period to the assigned IP will end at 11:00 PM on the first day of Visit 4.

On the second day of Visit 4 (Day 91), subjects who wish to smoke CC or use other nicotine/tobacco-containing products will be allowed to do so, but only after the end of 24-hour urine collection and after spirometry and sampling for CYP2A6 activity have been performed.

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

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

During the confinement and ambulatory settings:

- Any subject, who wants to attempt to quit using any tobacco products during the study taking into account the outcome from the Prochaska "Stages of Change" Questionnaire, will be encouraged to do so and will be referred to appropriate medical services. This will not affect subject's financial compensation and the subject will remain in the study.

- <u>The Safety Follow-up Period (from Discharge at Visit 4 until the end of the Safety Follow-up Period):</u>

  After Discharge at Visit 4 or the date of early termination, subject will enter a 28-day Safety Follow-up Period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the study. At the end of the Safety Follow-up Period, all ongoing AEs will be documented as "ongoing" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner for follow-up on ongoing AEs.

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

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

The individual end of study (EOS) date for a subject is defined as either the Discharge at Visit 4 or the date of early termination followed by the 28-day Safety Follow-up Period.

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

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 1.2, a candidate RRP. The comparator in this study will be CC.

The exposure period in confinement will provide information on exposure reductions achieveable in a well-controlled environment with full control on daily CHTP 1.2/CC consumption. The exposure period in the ambulatory setting will provide information on reduction of BoExp to selected HPHCs and related changes in selected clinical risk endpoints and functional endpoints when CHTP 1.2 is used in a real world setting. The choice of HPHCs to be assessed in this study is derived from the WHO [11] and the draft guidance on "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke" [12].

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 [11]. Exposure to 5 HPHCs (acrolein, CO, 1,3-butadiene, benzene, and NNK) among these 9 priority HPHCs will be assessed by measuring their respective BoExp as primary endpoints.

The BoExp for acrolein, CO, 1,3-butadiene, and benzene will be tested after 5 days of exclusive use of CHTP 1.2 and CC. The following characteristics apply to these selected BoExp:

- They are several-fold higher in smokers than in smokers abstinent from smoking [13].
- 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 1.2.
- They were decreased in smokers who switched to an earlier prototype of CHTP 1.2 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).

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The BoExp for NNK, i.e., total NNAL was selected as primary endpoint after 90 days of exposure to CHTP 1.2 and CC because:

- This BoExp is tobacco specific [14], and exhibits, on average, an elimination half-life of 10 to 15 days. Therefore, the 90 days of exposure are sufficient to reach the steady state with CHTP 1.2 and CC (4 to 5 times the half-life will lead to less than 5% of the original exposure levels after 90 days).

In addition to the 9 mandated lowering HPHCs recommended to be measured by WHO list, the FDA has listed 9 additional HPHCs for reporting to FDA (in total 18 HPHCs in cigarette smoke) [12]. 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 over the entire exposure period of exclusive use of CHTP 1.2 and CC.

Although the systemic responses to exposure to HPHCs in the cigarette smoke often result in elevation of the corresponding BoExp levels, the role of individual smoke constituents and their related BoExp on the development of smoking-related diseases has not been fully understood [15]. The missing link to a better understanding of elevated BoExp levels might be found if any association between elevated BoExp levels and changes in clinical risk endpoints, functional endpoints, and/or the pathogenesis of smoking related diseases could be shown. Recently, it has been shown that several of the low-grade systemic clinical risk endpoints of oxidative stress and inflammation are positively correlated with BoExp such as COHb, 3-HPMA, NEQ, and total NNAL after exposure to the HPHCs in the cigarette smoke in adult cigarette smokers [15].

Oxidative stress and inflammation are pathophysiological networks related to various smoking related diseases such as arteriosclerosis, hypertension [16], chronic inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) [17, 18].

There is evidence indicating that smoking enhances oxidative stress, not only through the production of reactive oxygene species (ROS) in smoke but also through weakening of the adequate counterbalancing antioxidant defense systems pushing and sustaining the pathogenetic pair of oxidative stress and inflammation [19].

The following biomarkers of oxidative stress have been selected in order to evaluate the extent of oxidative stress in the CHTP 1.2 arm as compared to the CC arm:

- 8-Hydroxy-2'-deoxyguanosine (8-OHdG)

  Deoxyguanosine is one of the constituents of the deoxyribonucleic acid (DNA). Under conditions of oxidative stress, it is oxidized and converted to 8-OHdG. Urinary 8-OHdG is a biomarker of generalized cellular oxidative stress reflecting the result of DNA lesions

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[20]. It has been shown that levels of 8-OHdG are increased in smokers [21], and 8-OHdG excretion declined upon smoking cessation [22].

- The ratio of 8-epi-prostaglandin F2α (8-epi-PGF2α; oxidized form of prostaglandin F2α) to prostaglandin F2α (PGF2α; non-oxidized form of prostaglandin F2α).

  8-epi-PGF2α and PGF2α are prostaglandin-like compounds, known as isoprostanes, and are formed from the peroxidation of arachidonic acid, an ubiquitous polyunsaturated fatty acid, in membrane phospholipids [23]. The biosynthesis of 8-epi-PGF2α in humans occurs via excessive chemical lipid peroxidation (> 99%), and in a very small part, via enzymatic lipid peroxidation by prostaglandin-endoperoxide synthases. Using the ratio of 8-epi-PGF2α to PGF2α can help to distinguish biomarker synthesis pathways and thus to confirm the potential change in oxidative stress [24].

- 4-Hydroxy-2-nonenal (4-HNE).

  Oxidative degradation of polyunsaturated fatty acids (PUFAs) occurs under conditions of oxidative stress when the cellular antioxidant defense mechanisms are overwhelmed leading to the formation of electrophilic lipid peroxidation products such as 4-HNE. Study results reported in the literature show that levels of 4-HNE are elevated in smokers and decrease significantly following smoking cessation [25].

- Total anti-oxidant capacity (TAC).

  Decreased total anti-oxidant capacity is indicative of conditions associated with oxidative stress or increased susceptibility to oxidative damage [26]. The combined activity of all the compounds in biological fluids with chain breaking antioxidant activity, excluding the contribution of antioxidant enzymes and metal binding proteins, will be assessed in a TAC assay. It has been reported in several studies that the assay of TAC is able to discriminate smoking status and demonstrates reversibility upon smoking cessation [27].

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 1.2 use on the activity of this enzyme [28]. Cytochrome P450 2A6 activity, the enzyme involved in nicotine metabolism, will be assessed in this study to evaluate if the use of CHTP 1.2 impacts the activity of this enzyme.

Some clinical risk endpoints and functional endpoints have been selected in order to evaluate biological changes in the CHTP 1.2 arm as compared to the CC arm. Among the ones selected, some are well-known to be affected by smoking and to be reversible upon SA as follows:

- 11-DTX-B2 (a major stable metabolite of thromboxane A2, which elicits mainly platelet aggregation) was decreased after 1 week of SA [29] and after 5 days of use of another candidate MRTP [30].

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- Blood pressure, hs-CRP, fibrinogen, homocysteine, fasting blood glucose, LDL, HDL, TG, TC, hemoglobin A1c (HbA1c), waist circumference, sICAM-1, WBC count, Apo A1, Apo B, and 8-epi-PGF2α will be evaluated as risk markers [31, 32] for cardiovascular monitoring purposes. According to the literature, some of these clinical risk endpoints are known to be sensitive to smoking cessation: the levels of HDL increase when the levels of sICAM-1, WBC count, and 8-epi-PGF2α decrease following 1 to 3 months of smoking cessation [31, 33].
- Body weight as a mean increase of 4.5 kg is observed after 12 months of smoking abstinence with the most weight gain occurring within the first 3 months of quitting [34].
- Lung function including forced expiratory volume in 1 second (FEV_1), force vital capacity (FVC), maximum expiratory flow (25-75), and respiratory symptoms such as cough will be assessed in this study, as it has been shown that some of these parameters may be improved and are markers correlating with early but still reversible changes occurring in distal airway upon smoking [35, 36].

Among others, clinical risk endpoints such as 8-epi-PGF2α, 11-DTX-B2, WBC, hs-CRP, fibrinogen, have been found related, i.e., to coronary atherosclerosis [15].

Other parameters such as product evaluation, and subjective effects related to smoking including smoking urges and withdrawal symptoms, and the intent to use, will be evaluated.

Twenty-four hour-urine collection conducted in this study is the standard method to measure the levels of excretion of BoExp.

As part of the characterization of the study population it is important to measure variables that have been shown to be related to nicotine dependence and product reinforcing value. Based on prior tobacco research these factors include age, gender, ethnicity, educational and socio-economic status, tobacco use history, expectations of the effects of the products tested, nicotine exposure. In order to capture, these data, subjects will be asked questions about their socio-economic status on Day 4. Such data would allow comparing populations across studies.

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 HPHCs and their respective 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 [11] and the draft guidance on

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”Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke” [12]

- 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 validated, 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 used for this study, except the Cough-VAS Questionnaire, are available as validated questionnaires or linguistically validated questionnaires.

4.4 Study Duration

The entire study duration per subject will be 128 to 169 days, including a Screening Period of up to 42 days prior to Admission on Day -3, a 9-day confinement setting (Day -3 to Discharge on Day 6) followed by a 85-day ambulatory setting (from Discharge on Day 6 to Discharge at Visit 4), and a 28-day Safety Follow-up Period. The EOS of the entire study is the last individual EOS time point during the study.

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5 STUDY POPULATION

120 smoking healthy Caucasian female or male subjects who has smoked at least 10 non-menthol CCs per day for the last 6 weeks prior to Admission will be included in this study. Each sex and each of the smoking strata (smoking 10 to 19 CC/day vs. > 19 CC/day) will have a quota applied to ensure that they represent at least 40% of the study population.

The maximum number of CC smoked daily is not limited. Subjects must have been smoking for at least 10 years of smoking prior to the Screening Visit. There will be no brand restrictions of non-menthol CC. Smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/mL).

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 ≥ 28 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 the Screening Visit and Admission, respectively, based on self-reporting. The smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	X
6. The subject has been smoking at least for the last 10 years.	Effect	X	X

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Inclusion Criteria	Rationale	Screening	Admission (Day -3)
7. The subject does not plan to quit smoking in the next 6 months as assessed by Prochaska "Stage of Change" Questionnaire.	Safety	X	
8. The subject is ready to comply with the study protocol (e.g., to use CHTP 1.2).	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 significant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric or cardiovascular disorders or any other conditions that in the opinion of the investigators would jeopardize the safety of the participant or affect the validity of the study results.	Safety	X	
4. Abnormal findings on physical examination, in the medical history, or in clinical laboratory test results assessed as Grade 2 and deemed clinically significant by investigators or Grade 3 and higher (as per the Common Terminology Criteria for Adverse Events [CTCAE]).	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	

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Exclusion Criteria	Rationale	Screening	Admission (Day -3)
6. The subject has (FEV1/FVC) < 0.75 (post-bronchodilator) and reversibility in FEV1 (that is both > 12% and > 200 mL from pre- to post-bronchodilator values).	Safety	X	
7. The subject has a body mass index (BMI) < 18.5 or ≥ 32 kg/m^2.	Safety	X	
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 3 (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
12. The subject has a positive urine drug test.	Administrative	X	X
13. The subject has positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B or hepatitis C.	Safety	X	
14. The subject has donated or received whole blood or blood products within 3 months prior to Admission.	Safety		X

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

5.3 Discontinuation of Subjects from the Study

Discontinued subjects (i.e., enrolled subjects that do not complete the study) 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 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 the PI or designee:

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- The subject agrees to undertake the early termination procedures for safety assessments as defined in section 9.5, unless the subject refuses to perform the assessments.
- If applicable, the subject still consents for long-term biobanking (3 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 must be discontinued from the study for any of the following reasons:

- Withdrawal of informed consent
- Subject becomes an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent, sibling and child)
- 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 test (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
- Subject unwilling to use the product during the entire study duration after having done the product test

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

- Non-compliance to the study procedures based on the judgment of the Investigator
- Violation of eligibility criteria

During the exposure ambulatory period, subject will not be discontinued from the study for the use of nicotine/tobacco containing products other than the assigned product/regimen during the ambulatory period.

Until randomization, subjects can be replaced, however subjects that discontinue the study after randomization will not be replaced.

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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. When the PIs or designee(s) declare(s) a subject is lost to follow-up, the lost to follow-up date will be recorded.The date of of lost to follow up corresponds to the date of the end of study of the subject.

If the site has lost track of the subject but the subject has reached the maximum number of study days (Day 169), 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 on Day -3 will be considered as screen failures. Re-screening of subjects is not permitted.

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6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

- CHTP 1.2

CHTP 1.2 is a non-menthol tobacco stick which is comparable in shape and form, and is used in a similar manner to CC. To use CHTP 1.2, 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 1.2. During use, the tobacco in CHTP 1.2 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 1.2 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 1.2 is to substantially reduce the exposure to HPHCs and provide an acceptable alternative and product use experience in comparison with CC.

- 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. 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 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 1.2, the packs and cartons will be labeled “for investigational use only” and according to any additional local regulatory requirements.

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6.3 Use of Investigational Product(s)

Subjects will never be requested or forced to smoke or to use the CHTP 1.2 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) At the end of the Screening Visit, subjects will be instructed not to smoke in the morning prior to Admission on Day -3.

6.3.1 Admission Day (Day -3)

After Enrolment, all subjects will undergo a CHTP 1.2 product test. However, before smoking and the product testing, the sample for CYP2A6 activity has to be taken. If subject is not willing and ready to use CHTP 1.2 after the product test, he/she will be discontinued from the study and undergo early termination procedures, followed by a 28-day Safety Follow-up Period.

After the sample for CYP2A6 activity has been taken, and the product test has been performed, smoking *ad libitum* will be allowed throughout the day until 11.00 PM. All subjects will be allowed to continue smoking *ad libitum* their single preferred brand of usual CC.

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 in Confinement (from Day 1 until the Discharge on Day 6)

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

- CHTP 1.2 arm

Subjects randomized to the CHTP 1.2 arm will use exclusively CHTP 1.2 from Day 1, 06:30 AM onwards until the time of Discharge on Day 6.

- CC arm

Subjects randomized to the CC arm will continue smoking their CC from Day 1, 06:30 AM onwards until until the time of Discharge on Day 6.

At the end of the confinement period prior to Discharge, subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days.

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6.3.4 Exposure Period in the Ambulatory Setting (from Discharge on Day 6 until Discharge at Visit 4)

On the first day of Visit 2, Visit 3, and Visit 4, subjects in the CHTP 1.2 and CC arms will be allowed to use their assigned product from the time of check-in until around 11:00 PM. On the second day of Visit 2 and Visit 3 product use will be allowed from 06:30 AM onwards. The exposure period to the assigned IP will end at 11:00 PM on the first day of Visit 4.

On the second day of Visit 4 (Day 91), subjects who wish to smoke CC or use other nicotine/tobacco-containing products will be allowed to do so, but only after the end of 24-hour urine collection and after spirometry and sampling for CYP2A6 activity have been performed.

During the ambulatory visits (Visit 2, Visit 3, Visit 4) the use of CHTP 1.2 will be strictly forbidden for subjects in the CC arm.

Subject will not be discontinued from the study for the use of nicotine/tobacco containing products other than the assigned product/regimen during the ambulatory period.

6.3.5 Safety Follow-up Period (from Discharge at Visit 4 until End of the Safety Follow-up Period)

During the Safety Follow-up Period 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

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

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

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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 2:

Table 2 Description of Blinded Study Personnel

Blinded Study Personnel	End of Blinding Period
PMI and CRO Study Statisticians	After the SAP finalization or the database lock [a] whichever comes last.
PMI Data Manager	After the finalization of PMI blind database review [a].
PMI Clinical Scientist	After the finalization of PMI blind database review [a].

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

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

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

6.6 Investigational Product Accountability and Compliance

6.6.1 Dispensing Investigational Product

During the confinement period from Day -3 to Discharge at Day 6, CC, and from Day 1 onwards to Discharge at Day 6, CHTP 1.2, 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 1.2) use has to be documented from Day -3 until Discharge at Day 6.

During the ambulatory period, subjects in the CHTP 1.2 arm will be provided with CHTP 1.2. Up to two extra deliveries of CHTP 1.2 in between two visits, e.g., between Visit 2 and Visit 3, will be carried out. Subjects in the CC arm will buy their CCs and will not be reimbursed.

Subjects will have free access to their assigned product (CC or CHTP 1.2) during Visit 2, Visit 3 and the first day of Visit 4 of the ambulatory period.

On the second day of Visit 4 (Day 91), subjects who wish to smoke CC or use other nicotine/tobacco-containing products will be allowed to do so, but only after the end of 24-

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hour urine collection and after spirometry and sampling for CYP2A6 activity have been performed.

CHTP 1.2 will not be promoted for commercial distribution or test market.

6.6.2 Storage and Accountability

CHTP 1.2 and CC will be stored in a secured storage site with access limited to authorized personnel only. The study collaborator designated by the PI will be responsible for the storage and accountability of the IPs in accordance to Sponsor's requirements. CHTP 1.2 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).

During the confinement period subjects will return each used CHTP 1.2 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.

During the ambulatory period subjects will record daily product use in the product use diary and return any unused packs, empty packs and partially used packs of CHTP 1.2 to the site for accountability after check-in at the investigational site at Visit 2, Visit 3 and Visit 4.

On the first day of Visit 4, after the collection and check of empty/partially used CHTP 1.2 packs for accountability, partially used packs will be returned and/or new packs will be handed out to the subjects, if requested, for use until 11:00 PM at the latest. All packs must be returned to study staff at the end of the first day of Visit 4.

No IP accountability will be done for CC in the CC arm during the ambulatory period.

Unused CCs given to the site collaborators at Admission will be given back to the subjects at Discharge on Day 6.

6.6.3 Investigational Product Retention

Used and unused CHTP 1.2 will be destroyed or returned to the Sponsor upon study completion as per instructions which will be provided by the Sponsor in due time.

6.6.4 Adherence to Investigational Products

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

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During the ambulatory period, from Discharge on Day 6 until Discharge at Visit 4, subjects in both study arms will capture the number of the product used (e.g., menthol and non-menthol CC, CHTP 1.2, or any other tobacco /nicotine-containing products including nicotine replacement therapy [NRT]) in the product use diary on a daily basis. The product use diary will be supplied by Sponsor and distributed to the subjects by the study site collaborators. The data captured in the product use diary will serve as the method to assess adherence in both arms. On Day 6, the adherence to the assigned product will be ensured using both the accountability log (from 06:30 AM until Discharge) and the product use diary (in the subjects daily report of product use). In case of discrepancy between the log and the diary entries, the diary will be considered as the primary source data.

6.7 Restrictions

6.7.1 Smoking Restrictions

6.7.1.1 Screening Visit and Confinement Period

At the Screening Visit pre- and post-bronchodilator spirometry will be done at least 1 hour after having stopped smoking. At the end of the Screening Visit, subjects will be instructed not to smoke in the morning prior to Admission on Day-3. On the Admission Day, smoking will be allowed only after the blood drawing for CYP2A6 activity has been taken, on Day -2, only after the Cough Questionnaire has been completed, and on the Day of Discharge (Day 6) only after twenty four-hour urine collection of Day 5 and the Cough Questionnaire have been completed, and the blood drawing for CYP2A6 activity assessment has 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 1.2 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 1.2 or CC) in separate smoking rooms.

Using CHTP 1.2 or smoking CC will not be allowed during study procedures.

6.7.1.2 Ambulatory Period

Subjects in the CHTP 1.2 arm will be instructed to exclusively use CHTP 1.2.

On the first day of Visit 2, Visit 3, and Visit 4, subjects in the CHTP 1.2 and CC arms will be allowed to use their assigned product from the time of check-in until around 11:00 PM. On the

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second day of Visit 2 and Visit 3 product use will be allowed from 06:30 AM onwards. The exposure period to the assigned IP will end at 11:00 PM on the first day of Visit 4. On the second day of Visit 4 (Day 91), subjects who wish to smoke CC or use other nicotine/tobacco-containing products will be allowed to do so, but only after the end of 24-hour urine collection and after spirometry and sampling for CYP2A6 activity have been performed.

During the ambulatory visits (Visit 2, Visit 3, Visit 4) the use of CHTP 1.2 will be strictly forbidden for subjects in the CC arm.

6.7.2 Dietary Restrictions

6.7.2.1 Confinement Period

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)" [37].

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 the subject will be asked to drink a cup of coffee for one of the assessment of CYP1A2).

Subjects will not be 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 both 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.

A fasting state has to be observed for at least 10 hours prior to blood drawings for:

- Safety laboratory on Day -1 and Day 6
- Clinical risk endpoints' assessments in serum/plasma/blood on Day -1 and Day 6

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- Serum/plasma bio-banking samples for BoExp, clinical risk endpoints and other circulating proteins on Day -1 and Day 6
- Blood bio-banking for further transcriptomics, lipidomics and DNA methylation sequencing analyses on Day -1 and Day 6

6.7.2.2 Ambulatory Period

The above dietary restrictions are not applicable for the ambulatory period.

One day prior to Visit 2, Visit 3, Visit 4, and during the visit on site, subjects will be asked by the site staff to refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during Visit 4.

A fasting state has to be observed for at least 10 hours prior to blood drawing for:

- Safety laboratory at Visit 2, Visit 3 and Visit 4
- Clinical risk endpoints' assessments in serum/plasma/blood at Visit 2, Visit 3 and Visit 4
- Serum/plasma bio-banking samples for BoExp, clinical risk endpoints and other circulating proteins, at Visit 4
- Blood bio-banking for transcriptomics, lipidomics and DNA methylation sequencing analyses at Visit 4

6.8 Concomitant Medication

For the purpose of this study, no concomitant medication should be taken by the subjects from Screening until the end of the Safety Follow-up Period without informing the PI or designee. However, the PI is responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescribing of medication will be made in the best interests of the subject.

Concomitant medication and prior medications will first be assessed at the 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. It is at the discretion of the Investigator or designee to assess if the termination of such medication at the Screening Visit is medically justified and safe for the subject.

Any medication (except medication containing estrogen) with an impact on the CYP1A2 and CYP2A6 metabolism (as prescription and over-the-counter products) as presented below in

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Table 3 must be avoided and must not be used during the entire study until the Discharge at Visit 4. Prior to database lock, concomitant medication will be reviewed according to their potential impact on CYP1A2 and CYP2A6 activity and assessed for their potential impact on the study results.

Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (including over-the counter products) is not allowed, as all of them could interfere with clinical risk endpoints such as 11-DTX-B2. Acetaminophen will be allowed at a daily total dose of up to 3000 mg.

If the use of a concomitant medication cannot be avoided for the subject's safety, it must be fully documented in the source document and transcribed into the case report form [CRF] (for details, see section 7.3.6). Concomitant medications should be followed up with the PI on an ongoing basis.

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 CRF.

Supplemental antioxidant nutrients such as β-carotene, α-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, vitamin E (α-tocopherol, γ-tocopherol), vitamin C and selenium with an impact on the clinical risk enpoints to oxidative stress must be avoided and should not be used during the entire study until the Discharge at Visit 4.

Table 3 Examples of Medications with Effects on CYP1A2 and CYP2A6 Activity

CYP1A2 Inhibitors [38]	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

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CYP1A2 Inhibitors [38]	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 [38]	**Drug Class**
Carbamazepine	Anticonvulsant
Phenobarbital	Anticonvulsant, barbiturate
Primidone	Anticonvulsant, barbiturate
Rifampin	Antibiotic, antitubercular agent
CYP1A2 Substrates [38]	**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
Flutamide	Antineoplastic agent, antiandrogen
Fluvoxamine	Antidepressant, selective serotonin reuptake inhibitor
CYP1A2 Substrates [38]	**Drug Class**
Guanabenz	Antihypertensive, central Alpha-2 adrenergic agonist
Mexiletine	Antiarrhythmic agent, class Ib

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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 [38]	**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 [38]	**Drug Class**
Amobarbital	Barbiturate
Pentobarbital	Anticonvulsant, barbiturate
Phenobarbital	Anticonvulsant, barbiturate
Rifampin	Antibiotic, antitubercular agent
Secobarbital	Barbiturate

CYP2A6 Substrates [38]	**Drug Class**
Dexmedetomidine	Alpha-2 adrenergic agonist, sedative

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Ifosfamide	Antineoplastic agent, alkylating agent

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

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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).

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 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.

Additionally, subjects will be asked to provide their separate consent for the use of the 8-iso-PGF2α/ PGF2α analysis, performed on already collected samples, for bioanalytical research purposes (section 1.3.23).

7.2 Smoking Cessation Advice and Debriefing

Each subject will be given advice on the risks of smoking, with smoking cessation (SC) advice, six times during the study: at the Screening Visit, at Admission on Day -3, at Discharge on Day 6, at Visit 2, Visit 3, and Visit 4. The form of a brief interview will be used according to current WHO recommendations [10]. Details of the interview will be recorded in the source document file. Information on the risk of smoking/SC 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 performed at Discharge from the study, together with information on the risk of smoking and SC advice to address any intended or unintended beliefs participants have about CHTP 1.2. 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 1.2 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.

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7.3.1 Demographic Data

Demographic data (gender, age, and race) will be collected.

See Appendix A for the time points 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 Habits

Subjects will be asked by the site collaborators the following questions about their smoking habits at the Screening Visit and on the Admission Day, and the answers will be recorded:

1. Have you smoked for at least the past 10 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)

   3 a. How many are non-menthol (check all, or 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/menthol CC until today? For example, any tobacco-based products or NRT, electronic cigarettes, or similar devices.
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)

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e. Never tried e-cigarettes

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

See Appendix A for the time points of assessment.

7.3.4 Product Preference

In order to perform a complementary analysis on subjects' preference, the following question will be asked to the subject;

"Which product would you prefer to be randomized to?":

- CHTP 1.2
- CC
- "No preference"

This question will be asked to all subjects on Day -3 after Enrolment, but will have no influence on randomization.

7.3.5 Demonstration and CHTP 1.2 Test

All subjects will have a demonstration of CHTP 1.2 at the Screening Visit. On Day -3 after Enrolment, subjects will have a product test using up to 5 sticks of CHTP 1.2. Subjects who are not willing and ready to use CHTP 1.2 will be discontinued from the study.

7.3.6 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical historywill be documented at the Screening Visit. Medical history is defined as any condition that started and ended prior to the Screening Visit. Any concomitant disease will be documented at the Screening Visit and on the Admission Day. A concomitant disease is defined as any condition that started before and was going on at the time of ICF signature.

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 the Screening Visit is also referred to as concomitant medication. This applies to both prescription and over-the-counter products.

Records of medication taken include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), total daily dose/unit (e.g., expressed in mg, mL, or IU), indication, the frequency, the start and (if applicable), the stop date (day, month

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and year). Any therapy changes (including changes of regimen) during the study are to be documented.

7.3.7 Physical Examination

A physical examination will be conducted and the assessment recorded.

See Appendix A for the time points of assessment.

7.3.8 Body Height and Weight

Body weight and height will be recorded at the Screening Visit, body weight will also be recorded at Admission and Day 6, at Visit 2, Visit 3, and Visit 4.

See Appendix A for the time points of assessment.

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

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

7.3.9 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.

Vital signs must be performed after a period of at least 15 minutes after having stopped using the allocated product.

See Appendix A for the time points of assessment.

7.3.10 Other Clinical Assessments

7.3.10.1 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.

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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 [39].

The spirometry tests will include the recording of FEV_1, FVC, FEV_1/FVC ratio, and FEF 25-75.

All spirometry testing must be performed at least 1 hour after having stopped using the allocated product (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.

See Appendix A for the time points of assessment.

7.3.10.2 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. QT interval will be corrected according to Federicia's formula. Every ECG has to be assessed as normal, abnormal – clinically not significant, or abnormal - clinically significant. A diagnosis has to be provided on the CRF for all ECGs assessed as abnormal – clinically significant. 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 the PI or designee.

See Appendix A for the time points of assessment.

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7.3.10.3 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, except for the analysis of 8-iso-PGF2α and PGF2α in plasma. The bioanalytical methods used will be documented in the bioanalytical plans and 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 in Exhaled breath and Blood

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).

  The CO breath test should be conducted in conjunction (i.e., within 30 minutes) with the blood sampling for COHb.

  See Appendix A for the time points of assessment.

- COHb test:

  Tests for COHb measurement will be performed at a designated laboratory.

  COHb assessments should be done in conjunction (i.e., within 30 minutes) with CO breath tests, where applicable.

  See Appendix A for the time points of assessment.

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7.4.1.2 Biomarker of Exposure to Nicotine in Plasma

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

See Appendix A for the time points of assessment.

7.4.1.3 Other Biomarkers of Exposure to HPHCs in Urine

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, and total NNAL
- Secondary endpoints: total 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, 3-hydroxybenzo(a)pyrene, 3-HMPMA, NEQ

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

7.4.2 Clinical Risk Endpoints

7.4.2.1 Cardiovascular Clinical Risk Endpoints

- In blood:

  Blood samples will be drawn according to the sample handling manual and laboratory manual in order to measure:

  - In serum: hs-CRP, LDL, HDL, Apo A1 and Apo B, sICAM-1, MPO
  - In plasma: fibrinogen, homocysteine
  - In blood: HBA1c

  No additional blood samples are required for the evaluation of blood glucose, TG, TC, WBC, and platelet count as clinical risk endpoints as they are measured as part of the safety parameters (section 7.5.1). As the analysis methods for hematology and clinical chemistry parameters are established and in use, no analytical plans and the respective analytical reports for platelet count, fasting glucose, total cholesterol and triglycerides will be generated, with the exception of WBC, for which the templates for the analytical plan and the respective report are already available.

  See Appendix A for the time points of assessment.

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- In urine:

  11-DTBX-B2 will be measured in 24-hour urine collection samples as per the schedule of events (Appendix A).

  For normalization, 11-DTBX-B2 will be expressed as concentrations adjusted to creatinine measured in 24-hour urine.

7.4.2.2 Clinical Risk Endpoints to Oxidative Stress

- In blood:

  Blood samples will be drawn according to the sample handling manual and laboratory manual in order to measure:

  - In serum:

    4-HNE [a] and TAC

  - In plasma:

    8-epi-PGF2α and PGF2α

  See Appendix A for the time points of assessment.

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

- In urine:

  8-OHdG and 8-epi-PGF2α will be measured in 24-hour urine collection samples as per the schedule of events (Appendix A).

  For normalization, 8-OHdG and 8-epi-PGF2α will be expressed as concentrations adjusted to creatinine measured in 24-hour urine.

7.4.2.3 Other Clinical Risk Endpoints

- 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 [28].

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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 time points of assessment.

- 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 time points of assessment.

7.4.3 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 for the time points 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 according to Appendix A for the timepoints of assessment. Blood will be taken after no less than the 10 hours of fasting except at the Screening Visit (section 6.7.2). Parameters to be measured are listed in Table 4.

The hematology and clinical chemistry parameters total white blood cell count (WBC), platelet count, fasting glucose, total cholesterol, triglycerides are listed, among others, as selected cardiovascular clinical risk endpoints in secondary objectives.

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Table 4 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 (to be performed only in case of abnormal urine analysis results)

See Appendix A for the time points of assessment.

7.5.2 Serology

A test for hepatitis B surface antigen, hepatitis C virus and human immunodeficiency virus (anti-HIV 1/2 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 time points 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 time points 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).

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See Appendix A for the time points 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 time points of assessment.

7.5.6 Serum/Urine Pregnancy Test

All female subjects will have pregnancy testing. At the Screening Visit, pregnancy testing for all female subjects will be performed using the serum pregnancy test. At all other time points after the Screening Visit, pregnancy testing for all female subjects will be performed using the urine pregnancy test. Female subjects with a positive serum pregnancy test at the Screening Visit or a positive urine pregnancy test at Admission will not be enrolled and will be considered as screen failures. In case of any positive 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. At the Screening Visit, 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.

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

See Appendix A for the time points 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 and the serum pregnancy test at the Screening Visit 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) and laboratory manual. Safety laboratory samples will be destroyed as per the laboratory's standard procedures. All primary and back-up samples for the assessments of BoExp and clinical risk endpoints (except bio-banking samples) will be destroyed after the bioanalytical report has been finalized or the database has been locked,

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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 laboratory(ies) are listed in the Appendix B.

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 303 mL, which includes about 40 mL for safety and repeated analysis, about 36 mL for long-term storage of the bio-banking samples of biomarkers, clinical risk endpoints and other circulating proteins (only if additional consent is given), and about 57 mL for long-term storage bio-banking samples for transcriptomics, lipidomics and DNA methylation sequencing analyses (only if additional consent is given) (section 7.6.3).

The blood sampling for transcriptomics, lipidomics, and DNA methylation sequencing analyses, 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 cotinine screening test, urine drug screening, urine pregnancy test and safety urine analysis at the Screening Visit and on the Admission Day.

7.6.2.1 Confinement Exposure Period

Twenty four-hour urine will be collected from Day -2 to Day 5 (which will end after 24 hours ± 1 hour on Day 6) on site.

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. On Day 1, product use must not start prior to the end of urine collection of Day -1.

From Day -1 onwards, the 24-hour urine collection for the respective day will 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.

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7.6.2.2 Ambulatory Exposure Period

During the ambulatory visits, subjects will be asked by the site at their check-in of the first day of the respectives visits (Visit 2, Visit 3, and Visit 4) to empty their bladder shortly at 09:00 ± 30 minutes. This urine will be discarded but the timing of the void will correspond to the start of urine collection. After nearly 24-hours of urine collection, subjects will empty their bladder again on the second day of the respective visit, and this urine will be used as the final portion of the 24-hour urine sample.

7.6.2.3 Confinement and Ambulatory Exposure Period

During the collection period for both confinement and ambulatory exposure 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.

Spot urine sample of the around 10 mL to measure 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 as well as the measurement of the volume of 24-hour urine will be recorded by the site in a log.

For assessment of urine BoExp, creatinine for normalization of urine BoExp, sample bio-banking and urine mutagenicity, clinical risk endpoints, 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 on Day 5 in the 24-hour urine collection, the 24-hour urine collection starts on Day 5 and ends in the morning of Day 6 prior to Discharge.

See Appendix A for the time points 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 for possible later analysis of additional biomarkers, additional samples of urine (from the 24-hour urine collection) and serum/plasma/whole blood (approx. 36 mL of blood in total) will be collected as follows:

- Serum/plasma/whole blood will be collected on Day -1, Day 6 and Visit 4, respectively (approx. 36 mL of blood in total with approx. 12 mL of blood draw per time point. This is to obtain and store 2 x 1 mL of serum, 2 x 1 mL of plasma and 2 x 1 mL whole blood).
- Samples from the 24-hour urine will be collected from the urine collections that started on Day -1, Day 5, and Visit 4, respectively (5 tubes of 10 mL urine for each time point).

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These samples are intended for possible later analysis of additional biomarkers of exposure, clinical risk endpoints or any other circulating proteins. No genetic or transcriptomics testing will be performed on these samples.

If a subject gives consent for sample bio-banking of whole blood/plasma for further transcriptomics, plasma for lipidomics analyses, and whole blood for DNA methylation sequencing approx. 57 mL of blood will additionally be collected in total. On Day-1, Day 6 and at Visit 4, approx. 15 mL blood in total will be collected for transcriptomics with 5 mL each day. The 5 mL whole blood per each assessment will be split into 2 tubes of 2.5 mL each. For lipidomics analyses, approx. 12 mL blood in total will be collected on Day -1, Day 6 and at Visit 4 with 4 mL each day. The 4 mL of blood will be centrifuged, and the plasma aliquoted in 2 tubes of 500 µl each. For DNA methylation sequencing, approx. 30 mL blood in total will be collected on Day -1, Day 6 and at Visit 4 with 10 mL each day. The 10 mL whole blood per each assessment will be split into 2 tubes of 5 mL each.

The samples intended for sample bio-banking will be kept frozen and shipped to a central storage facility. After the final clinical study report (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, lipidomics and DNA methylation sequencing analyses 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 time points of assessment.

7.7 Other Study Procedures

7.7.1 Product Use Diary

A product use diary will be used for the documentation of the used CHTPs 1.2, CCs (menthol and non-menthol), used NRTs product, or the use of other nicotine/tobacco containing products. All subjects in both arms must complete this diary on a daily basis on and from Day 6 until the time of Discharge at Visit 4. Subjects will be trained by site staff in the use of this diary during the confinement period at the time the diary is delivered to the subject.

7.7.2 Questionnaires

The subject questionnaires listed in the following sections including the cough-VAS used in this study will be answered and assessed by the subject directly on the CRF Health device. All

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subject-reported outcome data as well as instructions will be provided in the subject's local language.

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 such symptoms are 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 time points of assessment.

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

7.7.2.1 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 [40].

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) with regards to CC at the Screening Visit and the assigned product at Visit 4. .

See Appendix A for the time points of assessment.

7.7.2.2 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 reflecting the cough symptoms in the last 24 hours will be conducted irrespective of the time of product use.

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

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

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

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.

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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 time points of assessment.

7.7.2.3 Modified Cigarette Evaluation Questionnaire (MCEQ, Modified Version)

Product evaluation will be assessed using the subject self-reported MCEQ [41]. 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 time points of assessment.

7.7.2.4 Questionnaire of Smoking Urges (QSU-brief)

To assess the urge-to-smoke, all subjects will be asked to complete a 10-item brief version of the QSU [42]. 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 [43]. The findings supported a multi-dimensional conceptualization of craving to smoke and demonstrated the utility of a brief multi-dimensional measure of craving [42].

See Appendix A for the time points of assessment.

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7.7.3 Intent to Use Questionnaire (ITUQ)

The ITUQ is a self-report questionnaire that assesses subjects' intention to use CHTP 1.2 in smokers switching from CC to CHTP 1.2. The ITUQ comprises 3 sets of items:

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

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

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

This item will be rated on an ordinal scale with 6 timeframe categories ranging from "Within one week" to "Never".

See Appendix A for the time points of assessment.

7.7.4 Prochaska "Stage of Change" Questionnaire: Intention to Quit Smoking

The Prochaska's "Stage of Change" Questionnaire will be used to assess the smokers' mental state for the intention to quit (Appendix C for staging algorithm; [44, 45]).There are 5 stages of change describing smokers and former smokers: 1. Precontemplation, 2. Contemplation. 3. Preparation. 4. Action. 5. Maintenance.

- In the "Precontemplation" stage, the individual does not recognize smoking as a problem
- In the "Contemplation" stage, the individual is gathering information about smoking, such as contacting a health care provider or a tobacco quit line for information on the effects of smoking or smoking cessation consequences. During this stage, the stress and inconvenience of quitting smoking is greater than the immediate and possible long-term health effects of continuing smoking
- In the "Preparation" stage, intention and behavior begin to come together and the subject is preparing to enter into action in the next 30 days. It is necessary for the subject to recognize the benefits of not smoking, before a subject can enter the "Action" stage and as a result, changes his/her smoking behavior

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- After six months of not smoking, the individual reaches the "Maintenance" stage when different skills may be needed to prevent relapse from smoking

See Appendix A for the time points of assessment.

7.7.5 Socio-Economic Status (SES)

As part of the characterization of the study population it is important to measure variables that have been shown to be related to nicotine dependence and tobacco product reinforcing value. Based on prior tobacco research these factors include age, gender, ethnicity, tobacco use history, educational as well as socio-economic status (SES).

SES information is recorded in similar manner in the clinical program, in behavioral research and will be eventually assessed in post-marketing studies once the product is commercialized. In order to predict and to evaluate the effect of alternative, potentially less harmful tobacco product use might have in adult smokers the SES constitutes an important demographic characteristic. SES data will be reported across the randomized clinical studies and will be collected in observational pre- and post-marketing studies.

At the Screening Visit the subjects will be notified about the SES assessments.

Subjects will be asked a series of questions related to their education, occupational status, size and annual income of their household. These data will be used to create a measure for SES that categorizes subjects into low, moderate and high SES [46]. If the subject does not want to answer the questionnaire, he/she will not be discontinued from the study.

See Appendix A for the time points of assessment.

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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 [47]), an AE is defined as any untoward medical occurrence in a subject administered an IP, which does not necessarily have a causal relationship with the IP. 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, whether or not it is considered related to the IP.

8.1.2 Serious Adverse Events

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

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

"Life-threatening" means that the subject was at immediate risk of death from the event that, had it occurred in a more serious form, might have caused death.

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, a 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.

8.1.3 Conditions Existent Before the Start of the Period of Collection (ICF Signature)

Clinical conditions that existed before the start of the period of collection (concomitant disease), and whose severity or frequency remained unchanged after that point, should not be considered AEs and should not be captured as such. This includes medical therapies or surgical interventions that had been planned before the start of the period of collection regardless of involving admissions to hospital, if the medical condition to be addressed did not worsen after

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the start of the collection period. Otherwise, any medical condition that existed before the start of the period of collection and whose severity or frequency increased after that point is to be captured as a non-serious AE or an SAE, depending on the seriousness criteria met.

8.2 Collection, Assessment and Follow-up of Adverse Events

8.2.1 Collection of Information

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE CRF, and on the SAE form.

AEs should be collected mainly via face-to-face interview with the subject through spontaneous reporting or by the use of consistent, open, non-directive questions from the investigational site collaborators (e.g., "Have you had any health problems since you were last asked? or "How have you been feeling since you were last asked?").

Information recorded will include: verbatim description of the AE, start and stop dates, 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, stabilized).

Information to be recorded about an AE/SAE should include, whenever possible, the verbatim description of the AE/SAE, onset and resolution dates and times, circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence.

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms. Otherwise, each one of those signs and/or symptoms should be reported separately as event terms.

8.2.2 Period of Collection

Any AEs which occur during the Screening period will be captured by the study site staff and assessed by the PI(s) or designee(s) in order to establish relationship to study procedures. Only the study procedures-related AEs will be reported in the CSR and in accordance with respective regulatory guidelines.

AEs (including SAEs) will be collected from the time of ICF signature until the EOS.

During a 28-day Safety Follow-up Period there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general,

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all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the study. At the end of the Safety Follow-up Period, all ongoing AEs will be documented as "ongoing" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner for follow-up on ongoing AEs.

Any AEs or SAEs that are ongoing at the end of the 28 days of the Safety Follow-up Period will be managed as described in section 8.2.6.

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

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

8.2.3 Intensity of Adverse Event

The Investigator must assess the intensity of each reported AE according to the following grading scale:

Mild: Easily tolerated, not interfering with normal everyday activities

Moderate: Interferes with normal everyday activities, but the subject is still able to function

Severe: Incapacitating and requires medical intervention

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

The Investigator must assess the causal relationship between the exposure to the IP and each of the reported AEs, using the classification system and the criteria described below. The same assessment must be made separately regarding the causal relationship between the study procedures and each of the reported AEs:

Not related: The temporal relationship of the adverse event to IP 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 adverse to IP administration makes a causal relationship possible, and concomitant medication, therapeutic interventions, or

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underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with information already recorded about the IP CHTP 1.2 in the current IB. The current IB provides further detail on signs or symptoms that might be expected with the use of the IP CHTP 1.2, including information relating to malfunction or misuse [51]. The assessment of expectedness with the IP CC will be based on the judgement of the PI relying on the available safety information on CC in the literature.

8.2.6 Follow-up of Non-Serious and Serious Adverse Events

Any non-serious AE that is ongoing during the Safety Follow-Up Period will be actively followed-up by the Investigator during that period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

At the end of the Safety Follow-Up Period, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for on them anymore by the Investigator. At that point, the Investigator will assess whether the subject should be referred to his/her General Practicioner to have their ongoing AEs addressed accordingly.

All SAE will be followed up by the Investigator or designee, despite their continuation after the end of the Safety Follow-Up Period, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

8.3 Reporting of Serious Adverse Events

Any SAE observed during the period of collection by any of the parties involved in this study (including the Investigational site personnel) must be reported by that party within 24 hours of first awareness to [redacted].

SAEs considered related to the IP CHTP 1.2 and observed by, or reported to, any of the parties involved in this study (including the Investigational site personnel) after the period of collection must also be reported by that party within 24 hours of first awareness to [redacted] for safety surveillance purposes. Such SAEs will not be included in the clinical study report.

All the SAE report forms must be either faxed or sent as an attachment to an e-mail message to [redacted]:

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[redacted]:

Fax number: +41[redacted]

E-mail: [redacted]

Address: [redacted]
Switzerland

As further information regarding an already reported SAE becomes available to any of the parties involved in this study, such follow-up information should be reported on a new SAE report form, marked as a follow-up report and submitted to [redacted] according to the same timelines described above. The follow-up SAE report form must include the minimum information required for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

The SAE report form to be used in this study is provided as a separate document. All SAEs will also be recorded on the relevant CRF page, in addition to the SAE report form.

The PI or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the local Independent Ethic Committee (IEC) according to local regulations.

8.4 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the PI and assessed for clinical significance according to its severity. A clinically significant abnormal laboratory test result detected at the Screening Visit must be recorded as a concomitant disease. A clinically significant abnormal laboratory test result detected after the Screening Visit, but within the Screening Period, must be recorded as a concomitant disease or an AE based on the judgement of the PI. A clinically significant abnormal result detected after the Screening Period must be recorded as an AE (or linked to a concomitant disease), and handled according to the directions in sections 8.2 and 8.3. The severity of AEs representing clinically significant abnormal laboratory results should be assessed using the grading scheme shown in Appendix E. Whenever that grading scheme is not available for the laboratory result of concern, the PI should assess the severity and the clinical significance of that result using his/her medical judgment.

The principles for assessing and reporting abnormal laboratory test results, **emerging after the Screening Period**, using the grading scheme shown in Appendix E, is the following:

- All **Grade 1** abnormal laboratory value will be evaluated by the Investigator taking into account the value of the test of concern at Baseline and its clinical significance. If

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considered to be clinically significant, the Investigator must report it as an AE, or link it to a reported AE or to a concomitant disease.

- All **Grade 2** and higher abnormal laboratory value must be reported as an AE, or linked to an AE or a concomitant disease.

If there is any **worsening** in grade, the Investigator must report this worsening 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 [45] (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.

8.5 Collection, Follow-Up and Reporting of Pregnancies

8.5.1 Period of Collection and Follow-up

Pregnancies detected between the signature of the ICF and the Enrolment will lead to screen failure of the subject. In that situation, 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 PI or designee after the EOS of the subject, 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 exposure to IP.

8.5.2 Reporting of Pregnancies

A dedicated pregnancy form will be used to report reportable cases of pregnancy. The PI will complete that form (provided as a separate document) for all reportable pregnancies that are diagnosed (including positive serum or urine pregnancy tests).

The procedure to report a pregnancy and provide any additional/follow-up information to [redacted] must be followed in the same manner and within the same timelines as described for a SAE (section 8.3).

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The PI or designee is responsible for submitting to the local IEC any pregnancy report, 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 9.5 as soon as possible, and will enter the 28-day Safety Follow-up Period. The follow-up of these events will be performed according to section 8.2.6.

8.7 Investigational Product Malfunction and Misuse

During the confinement period, any occurrences of CHTP 1.2 malfunction ([redacted]) or misuse (use not in accordance with its label and instruction) by a subject, will be documented by the PI or his designee using a product issue log.

During the ambulatory visits at site, the PI or his designee will also collect information about CHTP 1.2 malfunction or misuse having occurred during the ambulatory period days between the ambulatory visits. In case the site is aware of a device event having occurred during the ambulatory period and some information is missing, only the available information as best recalled by the subject will be recorded on the issue log.

Investigational product misuse may result in use-related hazards.

Furthermore, any misuse or malfunction of CHTP 1.2 that leads to an AE/SAE will be handled with the same processes as described above for the reporting of AE/SAE.

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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.

Site personnel will adhere to the site's standard operating procedures (SOPs) for all activities or otherwise specified by the protocol. Appropriate medical advise will be provided to the subject in case of any medical findings requiring health care.

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 5 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 5 Time Schedule – Screening Visit (Day -45 to Day -4)

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)	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Screening**	
During the visit	√	Clinical laboratory parameters (hematology, clinical chemistry)	
During the visit		Safety urine analysis	
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 and medical history collected	
During the visit		Concomitant disease, prior and concomitant medication	
During the visit		Prochaska Questionnaire (Intent to Quit)	
During the visit		FTND Questionnaire	
During the visit		Questions about smoking habits	
During the visit		Identification of currently used CC brand	
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, at least 15 minutes after having stopped smoking
During the visit	√	Serum pregnancy test (all females)	
During the visit		Physical examination, height and weight, and calculated BMI	
During the visit		Urine drug screening	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Screening**	
During the visit		Urine cotinine screening	
During the visit		Alcohol urine or breath test	
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	See section 5
During the visit		CHTP 1.2 product demonstration	

Abbreviations: AE = Adverse event; CC = Combustible cigarette; CHTP 1.2 = Carbon Heated Tobacco Product 1.2; 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 6 shows the assessments that will be performed on the day of Admission (Day -3). A subject is considered as being enrolled once he/she is declared for being enrolled in the IxRS.

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Table 6 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 urine or breath test	Prior to Enrolment
During the visit		Prior/concomitant medication	Prior to Enrolment
During the visit		Questions about smoking habits	Prior to Enrolment
During the visit		Identification of currently used CC brand	Prior to Enrolment
During the visit		Inclusion/exclusion criteria	All eligibility criteria must be checked. Prior to Enrolment
During the visit		Enrolment	
During the visit		Physical examination, body weight, and calculated BMI	After Enrolment
During the visit		Waist circumference	After Enrolment
Prior to 11:30 AM	√	CYP2A6 activity in plasma	After Enrolment. Prior to smoking and the product testing
		Product test for CHTP 1.2 (Use up to 5 CHTPs 1.2)	After Enrolment. Subjects who are unwilling to use the product during the entire study duration will be discontinued from the study
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position
During the visit		CO breath test	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Admission (Day -3)**	
During the visit		Information on the risks of smoking, smoking cessation advice and debriefing.	
During the visit		Question on Product Preference	After Enrolment
During the visit		AE/SAE recording	At any time of the day
During the visit		Collection of used CC butts	For accountability
During the visit		Collection of CHTP 1.2 used for the product test	For accountability

Abbreviations: AE = Adverse event; BMI = Body mass index; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; SAE = Serious adverse event.

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

Table 7 shows the assessments that will be performed on Day -2.

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.

Table 7 Time Schedule – Day -2

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -2)**	
6:30 AM		Start of smoking CC	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
Prior to 11:30 AM		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.

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -2)**	
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to smoking
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped smoking
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
8:00 PM - 11:00 PM		ITUQ Questionnaire	
8:00 PM - 11:00 PM		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ 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 = Combustible cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; ITUQ = Intent to Use Questionnaire; QSU–brief = Questionnaire of Smoking Urges (brief version); MCEQ = Modified Cigarette Evaluation Questionnaire; SAE = Serious adverse event.

Table 8 show the assessments that will be performed on Day -1

Table 8 Time Schedule – Day -1

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -1)**	
6:30 AM		Start of smoking	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -1)**	
Prior to 11:30 AM		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.
Prior to 11:30 AM		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
Prior to 11:30 AM		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		ECG	At least 10 minutes in supine position prior to recording
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to smoking
Prior to 11:30 AM	√	Bio-banking for BoExp, clinical risk endpoints and other circulating proteins, and transcriptomics, lipidomics and DNA methylation sequencing	If additional consent is signed. After at least 10 hours of fasting
Prior to 11:30 AM	√	Clinical laboratory parameters* (hematology, clinical chemistry) and cardiovascular clinical risk endpoints (hs-CRP, MPO, fibrinogen, homocysteine, LDL, HDL, HbA1c, sICAM-1, Apo A1, Apo B, 8-epi-PGF2α, PGF2α), clinical risk endpoints of oxidative stress (4-HNE, TAC)	After at least 10 hours of fasting. * Blood glucose, TG, TC, WBC, platelet count from safety will be also evaluated as clinical risk endpoints

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Baseline Period (Day -1)**	
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
After 11:30 AM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the the cup of coffee.
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 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		QSU brief Questionnaire	
8:00 PM-11:00 PM		MCEQ Questionnaire	
11:00 PM		End of smoking period	
6:30 AM-11:15 PM		Collection of used CC butts	For accountability
		Randomization	Day -1

Abbreviations: 4-HNE = 4-hydroxy-2-nonenal; AE = Adverse event; Apo A1 = Apolipoprotein A1; Apo B = Apolipoprotein B; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; CYP2A6 = Cytochrome P450 2A6; ECG = Electrocardiogram; HbA1C = Hemoglobin A1C; HDL = High density lipoprotein; hs-CRP = High sensitive C-reactive protein; LDL = Low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MPO = Myeloperoxidase; QSU–brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event; sICAM-1 = Soluble inter-cellular adhesion molecule-1; TAC = Total anti-oxidant capacity; TC = Total cholesterol; TG = Triglycerides; VAS = Visual Analogue Scale; WBC = White blood cell

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9.2.3 Exposure Period (Days 1 to 5)

Table 9 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 2.

Table 9 Time Schedule – Day 1

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
		Allocation to study arm	
6:30 AM		Start of use of IPs	
Prior to 11:30 AM		AE/SAE recording	
Prior to 11:30 AM		Concomitant medications	
Prior to 11:30 AM		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.
Prior to 11:30 AM		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
Prior to 11:30 AM		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)
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using IP
Prior to 11:30 AM		Assessment of cough (VAS)	Has to be done prior to allocated IPs

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 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		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ 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 1.2	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; IP = Investigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU–brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event; VAS = Visual Analogue Scale

Table 10 shows the assessments that will be performed 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 10 Time Schedule – Day 2

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 2**	
6:30 AM		Start of use of IPs	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 2**	
Prior to 11:30 AM		End of 24-hour urine sample collection for Day 1	The urine is collected for 24 hours ±1 hour.
Prior to 11:30 AM		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
		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, at least 15 minutes after having stopped using IP
Prior to 11:30 AM		Assessment of cough (VAS)	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 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		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ 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 1.2	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; IP =

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 2**	

Investigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU–brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event; VAS = Visual Analogue Scale

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Table 11 shows the assessments that will be performed 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 11 Time Schedule – Day 3

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 3**	
6:30 AM		Start of use of IPs	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
Prior to 11:30 AM		End of 24-hour urine sample collection for Day 2	The urine is collected for 24 hours ±1 hour.
Prior to 11:30 AM		Start of 24-hour urine sample collection of Day 3.	The start of 24-hour urine collection of Day 3 should be subsequent to the end of 24-hour urine collection of Day 2
Prior to 11:30 AM		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, at least 15 minutes after having stopped using IP
Prior to 11:30 AM		Assessment of cough (VAS)	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 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		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ Questionnaire	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 3**	
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 1.2	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; IP = Investigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU–brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event; VAS = Visual Analogue Scale

Table 12 shows the assessments that will be performed 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 12 Time Schedule – Day 4

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 4**	
6:30 AM		Start of use of IPs	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
During the visit		SES Questionnaire	
Prior to 11:30 AM		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
Prior to 11:30 AM		Start of 24-hour urine sample collection of Day 4.	The start of 24-hour urine collection of Day 4 should be subsequent to the end of 24-hour urine collection of Day 3

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 4**	
Prior to 11:30 AM		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
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using IP
Prior to 11:30 AM		Assessment of cough (VAS)	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 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		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ 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 1.2	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 =Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; IP = Investigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU-brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event; SES = Socio-Economic Status Questionnaire; VAS = Visual Analogue Scale

Table 13 shows the assessments that will be performed on Day 5.

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

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Table 13 Time Schedule – Day 5

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 5**	
6:30 AM		Start of use of IPs	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
Prior to 11:30 AM		End of 24-hour urine sample collection for Day 4	The urine is collected for 24 hours ±1 hour.
Prior to 11:30 AM		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
Prior to 11:30 AM		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.
Prior to 11:30 AM		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using IP
Prior to 11:30 AM	√	Cardiovascular clinical risk endpoints/Biomarkers of oxidative stress (8-epi-PGF2α, PGF2α), clinical risk endpoints of oxidative stress (4-HNE, TAC)	After at least 10 hours of fasting.
Prior to 11:30 AM		Assessment of cough (VAS)	
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 9:30 PM (approx. 8:00 PM ± 1.5 hour)		CO breath test	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 5**	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 hour)	√	COHb in blood	
In the evening prior to 9:30 PM (approx. 8:00 PM ± 1.5 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		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ 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 1.2	For accountability

Abbreviations: AE = Adverse event; BoExp = Biomarker (s) of exposure; CAF = Caffein; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; IP = Investigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU–brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event; VAS = Visual Analogue Scale

Table 14 shows the assessments that will be performed on Day 6, prior to Discharge from the study unit.

Table 14 Time Schedule – Day of Discharge (Day 6)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 6**	
6:30 AM		Start of use of IPs	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
		End of 24-hour urine sample collection for Day 5	The urine is collected for 24 hours ±1 hour

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 6**	
		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 ± 1.5 hour	√	Clinical laboratory parameters* (hematology, clinical chemistry), cardiovascular clinical risk endpoint: sICAM-1	After at least 10 hours of fasting * Blood glucose, TG, TC, WBC, platelet count from safety will be also evaluated as clinical risk endpoints
06:29 AM ± 1.5 hour	√	CYP2A6 activity in plasma	Has to be done prior to use of IPs
06:29 AM ± 1.5 h	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
06:29 AM ± 1.5 hour		Spirometry pre- and post-bronchodilatator (recording of FEV_1, FVC, FEV_1/FVC)	Has to be done prior to use of IPs 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 BoExp, clinical risk endpoints and other circulating proteins, and transcriptomics, lipidomics and DNA methylation sequencing	If additional consent is signed After at least 10 hours of fasting

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 6**	
Prior to 11:30 AM		Assessment of cough (VAS)	
Before Discharge		ITUQ Questionnaire	
Before Discharge		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using IP
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.	
Before Discharge		Distribution of product use diary	To be completed by the subject every day from time of Discharge on Day 6 until next visit. All CHTPs 1.2, CC and any tobacco/nicotine containing products have to be recorded
6:30 AM - Discharge		Collection of used CC butts	For accountability
6:30 AM - Discharge		Collection of used CHTP 1.2	For accountability
		Discharge at Day 6	

Abbreviations: 4-HNE = 4-hydroxy-2-nonenal; AE = Adverse event; Apo A1 = Apolipoprotein A1; Apo B = Apolipoprotein B; BMI = Body mass index; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CYP2A6 = Cytochrome P450 2A6; ECG = Electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; HbA1C = Hemoglobin A1C; HDL = High density lipoprotein; hs-CRP = High sensitive C-reactive protein; IP = Investigational product; ITUQ = Intent to Use Questionnaire;

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 6**	

LDL = Low density lipoprotein; SAE = Serious adverse event; sICAM-1 = Soluble inter-cellular adhesion molecule-1; TAC = Total anti-oxidant capacity; TC = Total cholesterol; TG = Triglycerides; VAS = Visual Analogue Scale; WBC = White blood cell

9.3 Ambulatory Period (from Time of Discharge on Day 6 to the Day 91 (the Second Day of Visit 4)

For Visit 2 (Day 30 and Day 31), Visit 3 (Day 60 and Day 61) and Visit 4 (Day 90 and Day 91), a time window of +/- 5 days will be allowed with respect to the day of randomization. The time of opening and end of the visit are given as an estimate.

Table 15 shows the assessments that will be performed on Day 30 (the first day of Visit 2) and Day 60 (the first day of Visit 3) of the ambulatory period.

Table 15 Time Schedule –The First Day of Visit 2 (Day 30), The First Day of Visit 3 (Day 60)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 30 / Day 60**	
Prior to 8:30 AM		Start of Day 30 (the first day of Visit 2) / Day 60 (the first day of Visit 3)	No product use restriction prior to the opening of the visit Product use will be allowed on site in the CHTP 1.2 and CC arm from the time of check-in in the morning to around 11:00 PM The use of CHTP 1.2 in smokers allocated to CC is forbidden
During the visit		AE/SAE recording	
During the visit		Concomitant medications	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 30 / Day 60**	
09:00 AM ± 30 min		Start of 24-hour urine sample collection for Day 30 (the first day of Visit 2) / Day 60 (the first day of Visit 3)	The subject must empty his/her bladder and discard the urine prior to starting urine collection. The urine is collected for 24 hours ±1 hour
During the visit		CO breath test	Irrespective of the time of product use
During the visit	√	COHb in blood	Irrespective of the time of product use
During the visit	√	Plasma nicotine and cotinine sample	Cotinine will be measured in the same assay as nicotine. No additional blood samples required
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using IP
During the visit		Physical examination, body weight, and calculated BMI	
During the visit		Urine pregnancy test (females only)	
8:00 PM - 11:00 PM		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ Questionnaire	
11:00 PM		End of use of IPs	
During the visit		Product use diary	To be completed by the subject. All IPs used including CHTPs 1.2, CC, and any tobacco/nicotine containing products have to be recorded
During the visit		Collection of empty/partially used CHTP 1.2 packs for accountability	At any time of the day Partially used packs will be returned to the subject

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 30 / Day 60**	

Abbreviations: AE = Adverse event; BMI = Body mass index; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; IP = Investigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU-brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event

Table 16 shows the assessments that will be performed on the second day of Visit 2 and of Visit 3 of the ambulatory period.

Table 16 Time Schedule – The Second Day of Visit 2 (Day 31), The Second Day of Visit 3 (Day 61)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 31 / Day 61**	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
		End of 24-hour urine sample collection for Day 30 (the first day of Visit 2) / Day 60 (the first day of Visit 3)	The urine is collected for 24 hours ±1 hour
		Urine sample to be taken from the 24-hour urine of Day 30 (the first day of Visit 2) / Day 60 (the first day of Visit 3)	Aliquots from 24-hour urine will be collected according to Table A2.
Prior to 11:30 AM	√	Clinical laboratory parameters* (hematology, clinical chemistry) and cardiovascular clinical risk endpoints (hs-CRP, MPO, fibrinogen, homocysteine, LDL, HDL, sICAM-1)	After at least 10 hours of fasting * Blood glucose, TG, TC, WBC, platelet count from safety will be also evaluated as clinical risk endpoints
Prior to 11:30 AM		Assessment of cough (VAS)	Irrespective of the time of IP use

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 31 / Day 61**	
Before Discharge		Safety urine analysis	
Before Discharge		Information on the risks of smoking, smoking cessation advice and debriefing.	
Before Discharge		Product use diary	To be completed by the subject every day from time of Discharge until next visit. All IPs used including CHTPs 1.2, CC, and any tobacco/nicotine containing products have to be recorded.
		Discharge from Visit 2 / Visit 3	

Abbreviations: AE = Adverse event; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; IP = Investigational product; SAE = Serious adverse event; VAS = Visual Analogue Scale

Table 17 shows the assessments that will be performed on the first day of Visit 4 of the ambulatory period.

Table 17 Time Schedule – The First Day of Visit 4 (Day 90)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 90**	
Prior to 8:30 AM		Start of Day 90 (the first day of Visit 4)	No product use restriction prior to the opening of the visit Product use will be allowed on site in the CHTP 1.2 and CC arm from the time of check-in in the morning to around 11:00 PM

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 90**	
			The use of CHTP 1.2 in smokers allocated to CC is forbidden
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
09:00 AM ± 30 min		Start of 24-hour urine sample collection for Day 90 (the first day of Visit 4)	The subject must empty his/her bladder and discard the urine prior to starting urine collection. The urine is collected for 24 hours ±1 hour
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
After 11:30AM	√	CYP1A2 activity in plasma	6 hours ±15 minutes after intake of the cup of coffee
During the visit		CO breath test	Irrespective of the time of product use
During the visit	√	COHb in blood	Irrespective of the time of product use
During the visit	√	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		Prochaska Questionnaire (Intent to Quit)	
8:00 PM - 11:00 PM		QSU brief Questionnaire	
8:00 PM - 11:00 PM		MCEQ Questionnaire	
8:00 PM - 11:00 PM		FTND Questionnaire	
11:00 PM		End of use of IPs	

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 90**	
During the visit		Product use diary	To be completed by the subject. All IPs used including CHTPs 1.2, CC, and any tobacco/nicotine containing products have to be recorded.
During the visit		Collection of empty/partially used CHTP 1.2 packs for accountability	At any time of the day Partially used packs will be returned and/or new packs will be handed out to the subject for use until 11:00 PM at the latest.
End of day		Collection of empty/partially used CHTP 1.2 packs used during the day for final accountability	All packs must be returned to study staff at the end of Day 90.

Abbreviations: AE = Adverse event; CAF = Caffein; CC = Combustible cigarette(s); CHTP 1.2 = Carbon Heated Tobacco Product 1.2; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; FTND = Fagerström Test for Nicotine Dependence; IP = Ivestigational product; MCEQ = Modified Cigarette Evaluation Questionnaire; QSU-brief = Questionnaire of Smoking Urges (brief version); SAE = Serious adverse event

Table 18 shows the assessments that will be performed on the second day of Visit 4 prior to Discharge from the ambulatory period.

Table 18 Time Schedule – The Second Day of Visit 4 (Day 91)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 91**	
		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 90 (the first day of Visit 4)	The urine is collected for 24 hours ±1 hour. The end of the 24-hour urine collection should be prior to smoking

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 91**	
			the first CC/using other nicotine/tobacco-containing products.
		Urine sample to be taken from the 24-hour urine of Day 90 (the first day of Visit 4)	Aliquots from 24-hour urine will be collected according to Table A2. Bio-banking for biomarkers (if additional consent is obtained)
Prior to 11:30 AM	√	Clinical laboratory parameters* (hematology, clinical chemistry) and cardiovascular clinical risk endpoints (hs-CRP, MPO, fibrinogen, homocysteine, , LDL, HDL, HbA1c, sICAM-1, Apo A1, Apo B, 8-epi-PGF2α, PGF2α‡), clinical risk endpoints of oxidative stress (4-HNE, TAC)	After at least 10 hours of fasting. * Blood glucose, TG, TC, WBC, platelet count from safety will be also evaluated as clinical risk endpoints ‡As of 01 June 2016 blood samples for 8-epi-PGF2α/PGF2α will no longer be collected.
Prior to 11:30 AM	√	Bio-banking for BoExp, clinical risk endpoints and other circulating proteins, and transcriptomics, lipidomics and DNA methylation sequencing	If additional consent is signed After at least 10 hours of fasting
Prior to 11:30 AM		Spirometry pre- and post-bronchodilatator (recording of FEV_1, FVC, FEV_1/FVC)	Has to be done prior to use of CC or other nicotine/tobacco-containing products 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

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 91**	
			post administration of salbutamol
Prior to 11:30 AM	√	CYP2A6 activity in plasma	Has to be done prior to use of CC or other nicotine/tobacco-containing products
Prior to 11:30 AM		Assessment of cough (VAS)	Irrespective of the time of CC or other nicotine/tobacco-containing products use
Before Discharge		ITUQ Questionnaire	
Before Discharge		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using CC or other nicotine/tobacco-containing products
Before Discharge		Physical examination, body weight, and calculated BMI	
Before Discharge		Waist circumference	
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 from Visit 4	

Abbreviations: 4-HNE = 4-hydroxy-2-nonenal; AE = Adverse event; Apo A1 = Apolipoprotein A1; Apo B = Apolipoprotein B; BMI = Body mass index; BoExp = Biomarker (s) of exposure; CC = Combustible cigarette(s); CYP2A6 = Cytochrome P450 2A6; ECG = Electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; HbA1C = Hemoglobin A1C; HDL = High density lipoprotein; hs-CRP = High sensitive C-reactive protein; IP = Investigational product; ITUQ = Intent to Use Questionnaire; LDL = Low density lipoprotein; MPO = Myeloperoxidase;

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 91**	

SAE = Serious adverse event; sICAM-1 = Soluble inter-cellular adhesion molecule-1; TAC = Total anti-oxidant capacity; TC = Total cholesterol; TG = Triglycerides; VAS = Visual Analogue Scale; WBC = White blood cell

9.4 Safety Follow-Up Period

All subjects participating in the product test on Day -3 will enter the 28-day Safety Follow-Up Period.

After Discharge at Visit 4 or the date of early termination, subject will enter a 28-day Safety Follow-up Period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site.

Any AEs or SAEs that are ongoing at the end of the 28 days of the Safety Follow-up Period will be managed as described in section 8.2.6.

9.5 Early Termination Procedures

Early termination procedures will be as follows, unless the subject refuses to do so:

Table 19 Time Schedule - Early Termination Procedures

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Early Termination**	
During the visit		AE/SAE recording	
During the visit		Concomitant medications	
During the visit	√	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 10 hours of fasting
During the visit		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

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Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Early Termination**	
			All post-bronchodilator spirometry testing will be performed 15 - 30 minutes post administration of salbutamol
During the visit		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 minutes in supine position, at least 15 minutes after having stopped using IP
During the visit		ECG	At least 10 minutes in supine position prior to recording
During the visit		Physical examination, body weight, and calculated BMI	
During the visit		Safety urine analysis	
During the visit		Urine pregnancy test (females only)	
During the visit		Information on the risks of smoking, smoking cessation advice and debriefing.	
During the visit		Discharge from the site	

Abbreviations: AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; SAE = Serious adverse event

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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 PI 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 PI 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 PI 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 PI 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 PI, 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.

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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's 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 PI 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 PI or designee understands and agrees to provide access to the necessary documentation and files.

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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 subject reported outcome (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 documents by the PI(s) or 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

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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 (DM) CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the DM-CRO. The DM- 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 DM-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:

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Adverse events, concomitant disease, medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Medications:	WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical classification system

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 DM-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".

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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 (smoking 10 to 19 CC/day vs. > 19 CC/day)
3. Product used category (to be further described in the SAP).

12.1.2 Definitions for Statistical Data Analysis

Baseline:

Unless specified, Baseline is defined as the last available time point prior to first product use in the Exposure Period.

12.1.3 Descriptive Statistics

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

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 CV will be presented in addition to the mean and SD.

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

The primary endpoints will be tested using a multiple testing procedure to preserve the overall alpha level by simultaneously testing the endpoints using a closed procedure with each test performed at the one-sided 2.5% type I error probability. 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 on Day 5 and in total NNAL after 90 days in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability.

Table 20 describes the expected coefficients of variation (CV) and mean ratios (MR) between CHTP 1.2 and the one control arm based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study that investigated exposure to selected smoke constituents in smokers switching from CC to smoking article cigarettes for 5 days, the YVD-CS01-EU study (ClinicalTrials.gov ID: NCT00812279) sponsored by PMI.

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Table 20 Expected Mean Ratios and Coefficients of Variation for CHTP 1.2/CC after 5 Days of exposure

	CHTP 1.2/CC MR (CV)
COHb	0.40 (0.32)
3-HPMA	0.30 (0.50)
MHBMA	0.15 (0.70)
S-PMA	0.20 (0.70)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = Combustible cigarettes; COHb = Carboxyhemoglobin; CV = Coefficients of variation; MHBMA = Monohydroxybutenyl mercapyuric acid; MR = Mean ratios; S-PMA = S-phenylmercapturic acid; CHTP 1.2 = Carbon Heated Tobacco Product 1.2.

Table 21 describes the expected coefficients of variation (CV) and mean ratios (MR) in total NNAL after 90 days between CHTP 1.2 and the one control arm based on a randomized, controlled, forced-switching, open-label, parallel-group, single-center study in 90 male and female adult smokers to evaluate six biomarkers of tobacco smoke exposure over a 12-week period of unrestricted smoking in the participants' normal life setting [48].

Table 21 Expected Mean Ratios and Coefficients of Variation for CHTP 1.2/CC after 90 Days of exposure

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

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

The power to detect a reduction was computed.

Table 22 describes the expected power to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.2 arm compared to the CC arm after 5 days of exposure and total NNAL after 90 days of exposure, with a one sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and, and 120 randomized subjects in a 2:1 ratio (80 in CHTP 1.2 arm and 40 in CC arm). It is assumed that a minimal number of subjects will be excluded from the PP set in confinement for both arms and CC in ambulatory, whereas at least 50% will remain in the PP set in ambulatory for CHTP 1.2, therefore a 2:1 randomization ratio was chosen.

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Table 22 Expected Power

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

The test-wise powers to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb on Day 5 and in total NNAL after 90 days in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU, and 120 randomized subjects in a 2:1 ratio (80 in CHTP 1.2 arm and 40 in CC arm) are described in Table 23.

Table 23 Test-Wise Power

Parameter	Test-Wise Power
COHb	96%
3-HPMA	>99%
MHBMA	>99%
S-PMA	>99%
Total NNAL	98%

Given the above calculation, the sample size was considered sufficient to have more than 80% power to detect a reduction of 50% or more in the levels of MHBMA, 3-HPMA, S-PMA, and COHb in CHTP 1.2 arm compared to the CC arm after 5 days of exposure, and in the levels of total NNAL in the CHTP 1.2 arm compared to the CC arm after 90 days of exposure, using a one sided test with 2.5% type I error probability.

12.3 Analysis Populations

The study population characteristics will be described on the Safety Population and on the Per-Protocol population. The per-protocol population will be the primary analysis set for biomarkers of exposure, clinical risk endpoints, FTND, MCEQ, Cough and QSU-brief. The Full Analysis Set will be the primary analysis set for exposure, compliance to randomization arm, Prochaska and SES. Exposure and questionnaires, as a secondary analysis, will be described by randomization arm and product used category (to be further described in the SAP) using the full analysis set.

Safety will be analyzed using the safety population.

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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 1.2 or CC, and have at least one valid non-safety assessment (CHTP 1.2, 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 1.2, irrespective of whether or not the subject was exposed post-randomization. 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
- Total NNAL level at Visit 4

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 after 5 days of exposure, and in total NNAL after 90 days in smokers switching from CC to the CHTP 1.2 as compared to smokers continuing to use CC, using a one-sided test with 2.5% type I error probability.

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12.4.2 Baseline Comparability

Not applicable.

12.4.3 Descriptive Summary

Primary endpoints will be summarized as described in sections 12.1.3 and 12.3.

12.4.4 Confirmatory Analyses

The hypothesis to be tested for each of the BoExp of the primary and secondary objectives that the geometric mean level on Day 5 of the BoExp (MHBMA; 3-HPMA; S-PMA; COHb) and at Visit 4 of the BoExp total NNAL, respectively, for CHTP 1.2 is lower relative to CC.

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

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

Where m1 and m2 are the geometric means of the BoExp levels on Day 5 and at Visit 4, respectively, for CHTP 1.2 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 6 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.

12.5 Secondary Safety Endpoint(s)

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.

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12.5.3 Descriptive Analysis

In general, secondary endpoints will be summarized as described in sections 12.1.3 and 12.3.

12.5.4 Safety Analysis

In general, all safety data will be listed and tabulated by product arm, using the approach described sections 12.1.3 and 12.3. Safety variables collected during the 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.

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

12.6.2 Baseline Comparability

Not applicable.

12.6.3 Descriptive Analysis

In general, exploratory endpoints will be summarized as described sections 12.1.3 and 12.3.

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12.7 Demographics and Baseline Characteristics

Demographic and other Baseline characteristics will be summarized as described sections 12.1.3 and 12.3. Formal statistical analysis will not be performed on Baseline demographic data.

12.8 Interim Analysis

There are no planned interim analyses.

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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] Poland Phone: +48 [redacted] Fax.: +48 [redacted] E-mail: [redacted]@biovirtus.eu *Satellite site:* BioVirtus Research Site Sp. z.o.o. [redacted] [redacted] Poland Phone: +48 [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] Lead Clinical Scientist	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com

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[redacted] Clinical Scientist	Phone: +41 [redacted] E-mail: [redacted]@contracted.pmi.com
[redacted] Biostatistician	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com
[redacted] Medical Safety Officer	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
[redacted] Clinical Study Manager	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]@pmi.com

13.1.3 Reception and Handling of SAE and pregnancy reports

Any reports of SAEs or pregnancies will be handled by:

[redacted]

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

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.

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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, lipidomics and DNA methylation sequencing analyses, 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, lipidomics and DNA methylation sequencing analyses 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.

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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 Enrolment 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.

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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 complied with as requested by local requirements.

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

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

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

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	Screening	Confinement Period									Ambulatory Period						Safety Follow-up [r]
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 [p]**	**30 [q]**	**31 [q]**	**60 [q]**	**61 [q]**	**90 [q]**	**91 [q]**	**91 to 119**
Questions about smoking habits	•	•															
Intention to quit smoking in the next 6 months using Prochaska's Questionnaire	•														•		
Identification of the current CC brand	•	•															
CHTP 1.2 demonstration	•																
CHTP 1.2 product test [e]		•															
Question on product Preference		•															
Collection of CC butts for accountability		•	•	•	•	•	•	•	•	•							
Collection of used CHTP 1.2 sticks for accountability		•			•	•	•	•	•	•							
Collection of empty/partially used CHTP 1.2 packs for accountability											•		•		•		
CO breath test [f]		•	•	•	•	•	•	•	•		•		•		•		
B: BoExp in blood: COHb [g]			•	•	•	•	•	•	•		•		•		•		

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	Screening	Confinement Period									Ambulatory Period						Safety Follow-up [r]
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 [p]**	**30 [q]**	**31 [q]**	**60 [q]**	**61 [q]**	**90 [q]**	**91 [q]**	**91 to 119**
B: BoExp to nicotine in plasma: nicotine, cotinine [h]				•	•	•	•	•	•	•	•		•		•		
U: All urinary BoExp in 24-hour urine (defined as primary and secondary endpoints, and BoExp to nicotine) (see Table A2)			•	•	•	•	•	•	•		•		•		•		
B: Serum: Clinical risk endpoints: hs-CRP, MPO, blood glucose, LDL, HDL,				•								•		•		•	
B: Plasma: Clinical risk endpoints: fibrinogen, homocysteine				•								•		•		•	
B: Serum: Clinical risk endpoint: sICAM-1				•						•		•		•		•	
B: Clinical risk endpoint: HbA1C				•												•	
B: Serum: Clinical risk endpoints: Apo A1, and Apo B				•												•	
B: Serum: Biomarkers of oxidative stress: 4-HNE, TAC				•					•							•	

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	Screening	Confinement Period									Ambulatory Period						Safety Follow-up [r]
Visit (Time Window)	**Screening Visit Visit 1**										**Visit 2 (Day 30 ± 5 days)**		**Visit 3 (Day 60 ± 5 days)**		**Visit 4 (Day 90 ± 5 days)**		
Study Day	**-45 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 [p]**	**30 [q]**	**31 [q]**	**60 [q]**	**61 [q]**	**90 [q]**	**91 [q]**	**91 to 119**
B: Plasma: Clinical risk endpoints/Biomarkers of oxidative stress: 8-epi-PGF2α, PGF2α [i]				●					●							●	
U: Clinical risk endpoints/Biomarkers of oxidative stress in 24-hour urine: 11-DTX-B2, 8-epi-PGF2α, 8-OHdG (see Table A2)				●	●					●		●		●		●	
Intake of a cup of coffee				●					●						●		
B: CYP1A2 activity				●					●						●		
B: CYP2A6 activity		●								●						●	
Product use diary [j]										●	●	●	●	●	●		
Intent to Use Questionnaire (ITUQ)			●							●						●	
QSU-brief Questionnaire [k]			●	●	●	●	●	●	●		●		●		●		
MCEQ (modified version) [l]			●	●	●	●	●	●	●		●		●		●		
Assessment of cough [m]			●	●	●	●	●	●	●	●		●		●		●	
AE/SAE recording	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

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

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

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

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

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

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

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

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

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

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

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

[i] As of 01 June 2016, samples for this endpoint will no longer be collected

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

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

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

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

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

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

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

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

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

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Table A2 Schedule for 24-hour Urine Collection Assessments

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

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

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

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

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Appendix B Participating Laboratories

[redacted]
USA
Phone: +1 [redacted]

[redacted]
Switzerland
Phone: +41 [redacted]

[redacted]
Poland
Phone: +48 [redacted]

[redacted]
Canada

Biobanking of samples:

[redacted]
Germany

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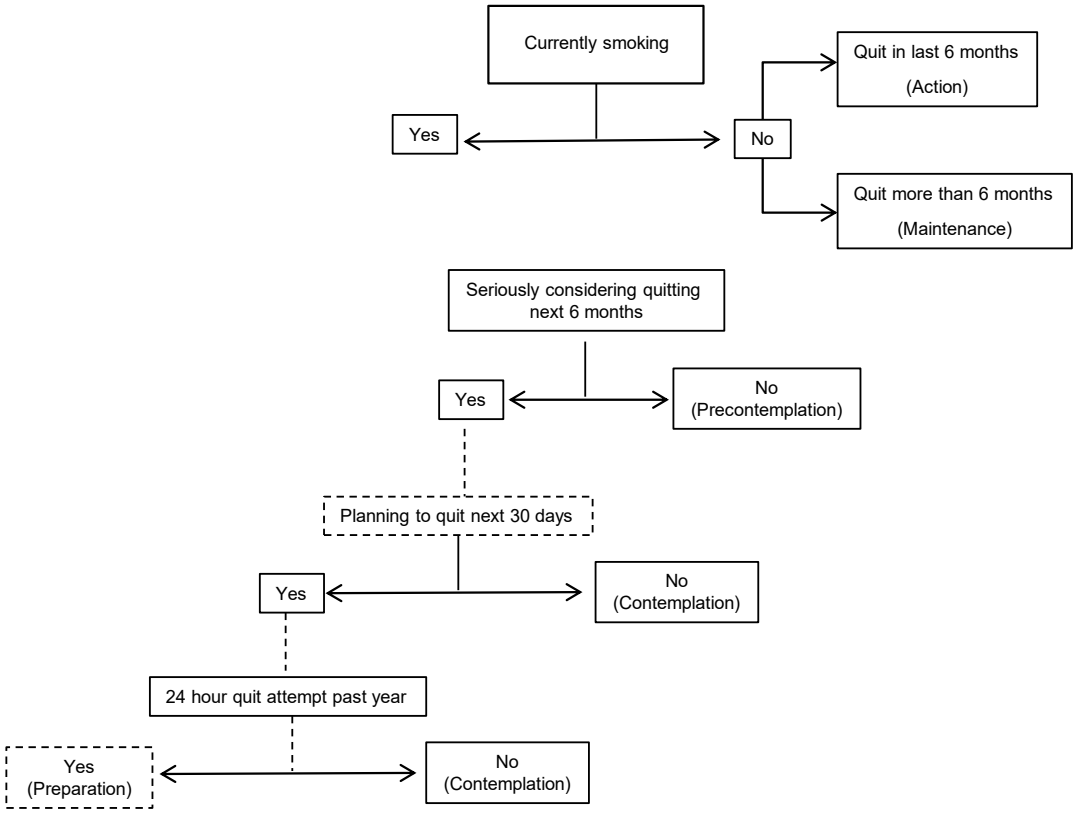
Appendix C Prochaska "Stage of Change" Questionnaire

The Prochaska questionnaire is structured as follows:



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The questionnaire to be asked is as follows, with the scoring sheet not to be read aloud:

Smoking algorithm for the classification of the stages of change for smoking cessation

Assessment:

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

Smokers only:

2. In the last year, how many times have you quit smoking for at least 24 hours? ___

3. Are you seriously thinking of quitting smoking?
   A) Yes, within the next 30 days
   B) Yes, within the next 6 months
   C) No, not thinking of quitting

Scoring Sheet (do not read to subject):

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

Smokers only:

2. In the last year, how many times have you quit smoking for at least 24 hours? -------

3. Are you seriously thinking of quitting smoking?
   A) Yes, within the next 30 days (PREPARATION STAGE if they have one 24-hour quit attempt in the past year, if there was no quit attempt in the past year, then CONTEMPLATION STAGE)
   B) Yes, within the next 6 months (CONTEMPLATION)

C) No, not thinking of quitting (PRECONTEMPLATION)

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Appendix D Summary of Biomarkers of Exposure to HPHC

HPHC [smoke phase]	HPHC List	Biomarker	Matrix	$t_{1/2}$
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
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)	Urine	10 to 18 days
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

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HPHC [smoke phase]	HPHC List	Biomarker	Matrix	$t_{1/2}$
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
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)

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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 [49] (mmol/L)	< LLN - 130	-	< 130 - 120	< 120
Sodium – Hypernatremia [49] (mmol/L)	> ULN - 150	> 150 - 155	> 155 – 160 hospitalization indicated	> 160
Potassium – Hyperkalemia [49] (mmol/L)	> ULN - 5.5	> 5.5 - 6.0	> 6.0 - 7.0 hospitalization indicated	> 7.0
Potassium – Hypokalemia [49] (mmol/L)	< LLN - 3.0	< LLN - 3.0; symptomatic; intervention indicated	< 3.0 - 2.5 hospitalization indicated	< 2.5
Glucose – Hypoglycemia [49] (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 [49] 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 [49]	> 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 [49] (g/dL) (g/L)	< LLN – 3 < LLN - 30	< 3 – 2 < 30 - 20	< 2 < 20	- -
Alkaline phosphatase increased [49]	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT/AST increased [49]	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN

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Serum Chemistry *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Gamma-glutamyl transferase (GGT) increased [49]	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Blood bilirubin increased [49] (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 [49]				
(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 [49]				
(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 significant.

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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 [49] (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 [49] (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 [49] (cell/mm^3)	 -	 > 4,000 – 20,000	 > 20,000	 -
Lymphocytes decrease [49] (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 [49] (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 [49] (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 significant.

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ABNORMAL LABORATORY VALUES RATING: URINALYSIS PARAMETERS

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Protein [49]	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 significant.

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