PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol P2M-PK-04-JP

Study title:	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile of the Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M) following single use in smoking, healthy subjects compared to menthol conventional cigarettes
Short name:	Nicotine pharmacokinetic profile of the CHTP 1.1 M
Registration number:	Not assigned
Product name:	Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M)
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	Version 2.0
Date:	18 May 2015
Authors:	[redacted], PhD, Clinical Scientist [redacted], MEng MSc, Biostatistician [redacted], MD, Medical Safety Officer

Amendment 1

SUMMARY OF CHANGES

The following administrative changes are issued as non-substantial amendments of the clinical study protocol P2M-PK-04-JP:

- Replacement of the current Medical Safety Officer [redacted], MD, PhD: The Medical Safety Officer duties have been assumed *ad interim* by [redacted], **MD** until 31 May 2015. As of the 1st June 2015, the responsible Medical Safety Officer will be [redacted], **MD, PhD, MFPM**. These administrative changes are reflected on the front page, in section 8.3 "Reporting and Follow-Up of Serious Adverse Events", in section 13.1.2 "Sponsor" and in section 13.1.3 "Other Responsibilities".
- The **contact details** of the local contract research organization [redacted] have changed due to relocation. These administrative changes are reflected in section 13.1.3 "Other Responsibilities".
- Replacement of the current Biostatistician [redacted], PhD: The Biostatistician duties have been assumed by [redacted], **MEng, MSc**. These administrative changes are reflected on the front page and in section 13.1.2. Sponsor.
- Replacement of the current Clinical Scientist [redacted], PhD: The Clinical Scientist duties have been assumed by [redacted], **PhD**. These administrative changes are reflected on the front page and in section 13.1.2. Sponsor.

SYNOPSIS

Sponsor:

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

Product Name:

Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M)

Study Title:

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

Study Number:

P2M-PK-04-JP

Short Study Title:

Nicotine pharmacokinetic profile of the CHTP 1.1 M

Objectives and Endpoints:

Primary Objective and Endpoints:

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

Endpoints:

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

Secondary Objectives and Endpoints:

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

   Endpoints:

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

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

   Endpoint:

   - t_{max}

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

   Endpoint:

   - $t_{1/2}$

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

   Endpoint:

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

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

   Endpoint:

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

6. To describe the levels of carbon monoxide (CO) exposure for the CHTP 1.1 M as compared to mCC.

   Endpoint:

   - CO exposure biomarkers: levels of exhaled CO and carboxyhemoglobin (COHb) in blood

7. To monitor the safety during the study.

Endpoints:

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

Additional study assessments (for baseline characteristics):

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

Study Hypothesis:

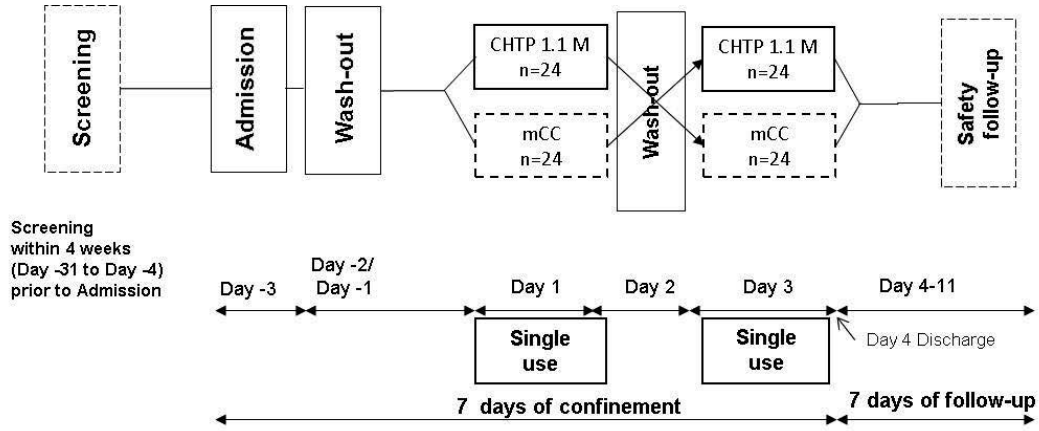
Given that the objective of this study is to determine the point estimate and precision of the ratio of the CHTP 1.1 M:mCC for C_{max} and $AUC_{(0\text{-last})}$, there is no statistical hypothesis to be tested.

Evaluation Criterion:

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

Study Design:

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



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

Figure 1 Study Flow Chart

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

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

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

Sequence 1: CHTP 1.1 M then mCC

Sequence 2: mCC then CHTP 1.1 M

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

From discharge on Day 4 until Day 11: a 7-day safety follow-up will be done for the recording of spontaneously reported AEs and SAEs (passive surveillance) and the active follow-up by the investigational site of AEs/SAEs ongoing at the time of discharge.

Study Population and Main Criteria for Inclusion:

A total of 48 healthy female or male Japanese currently smoking adult subjects following the main inclusion criteria:

- Subject is at a minimum 23 years of age
- Smoking, healthy subject as judged by the Investigator

- Subject does not plan to quit smoking in the next 3 months
- The subject is ready to accept interruptions to smoking for up to 6 days
- The subject is ready to accept using CHTP 1.1 M

Subjects will be randomized to 1 of 2 sequences. Each sex and each of the smoking level (ISO nicotine levels ≤ 0.6 mg and 0.6 to 1 mg) will have a quota applied to ensure they represent at least 40% of the total study.

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

Investigational Products:

- CHTP 1.1 M
- Subject's own supply of commercially available preferred single brand mCC

Study Duration:

The entire study per subject will last from 15 to 42 days, including a screening period of up to 28 days (Day -31 to Day -4) prior to Admission, and 7 days of confinement (Day -3 to discharge on Day 4). In the morning of Discharge (Day 4) examinations will be conducted. After Discharge, subjects will then enter a 7-day safety follow-up (until Day 11) for the recording of spontaneously reported AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site.

Statistical Methods:

All primary and secondary endpoints will be summarized with descriptive statistics. In addition, PK, subjective effects of smoking, and safety variables will be analyzed as follows.

Pharmacokinetics:

Only subjects without major protocol deviations that impact the evaluability of the data will be included in the PK analysis set.

Nicotine PK parameters will be derived from plasma nicotine data by non-compartmental analysis.

An analysis of variance (ANOVA) will be conducted on natural logarithmically transformed $AUC_{(0\text{-last})}$ and C_{max} endpoints. The model will include terms for sequence, subjects within sequence, product exposure, and period as fixed effect factors. The results of this analysis will be presented in terms of adjusted geometric least square means and 95% confidence intervals (CI) for CHTP 1.1 M:mCC ratio.

$AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}12)}$,$AUC_{(0\text{-}t')}$, and $t_{1/2}$ will be analyzed using the same approach adopted for the primary endpoints. The Hodges-Lehmann estimates of median t_{max} differences between the CHTP 1.1 M and mCC will be presented together with the 95% CI.

Subjective effects of smoking:

A mixed effects ANOVA using period, sequence, and product exposure as fixed effects and subjects within sequence as a random effect will be adopted to analyze the domain scores of the product evaluation (MCEQ) questionnaire, for the comparison between CHTP 1.1 M and mCC. The same model will be evaluated for the urge-to-smoke (QSU-brief), including the assessment time points as repeated measurements. The results will be presented in terms of least square means and 95% CI for the CHTP 1.1 M-mCC differences. Questionnaire scores will be summarized by product exposure, including the mean percent change from the value prior to T_0. The maximum percent decrease over time and the time to maximum percent decrease over time will be summarized by product exposure and analyzed using the Hodges-Lehmann method for the QSU-brief total score.

Safety Analysis:

The safety population will comprise all subjects who are exposed to the CHTP 1.1 M during the study, including the product test at Admission. Adverse event data will serve as the primary assessment of safety. Safety data will be listed and tabulated by sequence.

Sample Size:

A total of 48 subjects will be randomized.

48 subjects are needed to estimate the mean C_{max} parameter ratio between CHTP 1.1 M and mCC with a 80% probability of obtaining a margin of error (95% CI) of at most ±30%, assuming that the CHTP 1.1 M have a nicotine PK profile similar to mCC (C_{max} ratio equal to 1.00) and a 5% dropout rate.

The sample size of this study is based on our current understanding from the use of the Tobacco Heated System 2.2 Menthol (THS 2.2 Menthol), another PMI heated platform tobacco product, in the Japanese population where the within-subject coefficient of variation for nicotine C_{max} and $AUC_{(0\text{-last})}$ was found to be 60% and 50%, respectively.

TABLE OF CONTENTS

SUMMARY OF CHANGES 2
SYNOPSIS 3
TABLE OF CONTENTS 9
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 16
1 ETHICS AND REGULATIONS 20
1.1 Institutional Review Board Approval 20
1.2 Ethical Conduct of the Study 20
1.3 Subject Information and Consent 21
1.3.1 Informed Consent Form for Study Participation 21
1.3.2 Amendment to the Informed Consent Form 21
1.4 Good Clinical Practice and Regulatory Requirements 21
2 INTRODUCTION 23
2.1 Background 23
2.1.1 Smoking-Related Diseases and Harm Reduction Strategy 23
2.1.2 Description of the Product and Scientific Findings 23
2.2 Purpose of the Study 24
2.3 Anticipated Benefits and Risks 24
2.3.1 Anticipated Benefits 24
2.3.2 Anticipated Foreseeable Risks due to Study Procedures 24
2.3.3 Anticipated Foreseeable Risks due to Investigational Product (CHTP 1.1 M) 24
2.3.4 Unforeseeable Risks 25
3 STUDY OBJECTIVES AND ENDPOINTS 26
3.1 Primary Objective and Endpoints 26
3.2 Secondary Objectives and Endpoints 26
4 INVESTIGATIONAL PLAN 29
4.1 Overall Study Design and Plan 29
4.2 Rationale for Study Design and Control Group 30
4.3 Study Duration 31

4.4 Appropriateness of Measurement 31
5 STUDY POPULATION 32
5.1 Inclusion Criteria 32
5.2 Exclusion Criteria 33
5.3 Discontinuation of Subjects from the Study 36
5.4 Lost to follow up 37
5.5 Violation of Selection Criteria 37
6 INVESTIGATIONAL PRODUCTS 38
6.1 Description of Investigational Products 38
6.2 Packaging and Labeling 38
6.3 Use of Investigational Products 39
6.3.1 Admission (Day -3) 39
6.3.2 Investigational Period (Day -2 to Day 3) 39
6.3.3 Single Use of Products (Day 1 and Day 3) 39
6.3.4 Day of Discharge 40
6.3.5 Safety Period 40
6.3.6 Stopping Rules for Investigational Product 40
6.4 Method for Assigning Subjects to Sequences 40
6.5 Blinding 41
6.6 Investigational Product Accountability and Compliance 41
6.6.1 Dispensing Investigational Product 41
6.6.2 Storage and Accountability 41
6.6.3 Investigational Product Retention 42
6.6.4 Compliance to Investigational Products 42
6.7 Restrictions 42
6.7.1 Smoking Restrictions 42
6.7.2 Dietary Restrictions 42
6.7.3 Concomitant Medication 43
6.7.4 Other 44
7 STUDY PROCEDURES 45

7.1 Informed Consent Form 45
7.2 Smoking Cessation Advice and Debriefing 45
7.3 Support during Smoking Abstinence/Periods of Reduced Smoking 45
7.4 Clinical Assessments 46
7.4.1 Demographic Data 46
7.4.2 Identification of the Current Cigarette Brand 46
7.4.3 Smoking History and Willingness to Quit Smoking 46
7.4.4 Demonstration and CHTP 1.1 M Test 46
7.4.5 Medical History, Concomitant Disease, Previous and Ongoing Medications 47
7.4.6 Physical Examination 47
7.4.7 Body Height and Weight 47
7.4.8 Vital Signs 47
7.4.9 Other Clinical Assessments 48
7.4.9.1 Spirometry 48
7.4.9.2 Electrocardiogram 48
7.4.9.3 Chest X-ray 48
7.5 Biomarker Assessment 49
7.5.1 Biomarker of Exposure 49
7.5.1.1 Biomarker of Exposure to CO and COHb 49
7.5.1.2 Biomarkers of Exposure to Nicotine 49
7.5.2 CYP2A6 Activity 50
7.6 Laboratory Assessments 50
7.6.1 Clinical Chemistry, Hematology, and Urine Analysis for Safety Panel 50
7.6.2 Serology 51
7.6.3 Urine Drug Screen 51
7.6.4 Urine Cotinine Screening 51
7.6.5 Alcohol Breath Test 51
7.6.6 Urine Pregnancy Testing 51
7.7 Sample Handling, Storage, and Shipment 51
7.7.1 Blood Samples 51
7.7.2 Urine Samples 52

7.8 Questionnaires....52
7.8.1 Fagerström Test for Nicotine Dependence (FTND, revised version)....52
7.8.2 Assessment of Cough....52
7.8.3 Modified Cigarette Evaluation Questionnaire (MCEQ, modified version)....53
7.8.4 Questionnaire of Smoking Urges....53
8 ADVERSE EVENTS....54
8.1 Definitions....54
8.1.1 Adverse Events....54
8.1.2 Serious Adverse Events....54
8.2 Assessment of Adverse Events....54
8.2.1 Collection of Information....54
8.2.2 Period of Collection....55
8.2.2.1 Screening Period....55
8.2.2.2 Admission until End of Study....55
8.2.3 Intensity of Adverse Event....56
8.2.4 Relationship to Investigational Product and Relationship to Study Procedures....56
8.2.5 Expectedness....56
8.3 Reporting and Follow-Up of Serious Adverse Events....57
8.4 Reporting of Other Events Critical to Safety Evaluations....58
8.4.1 Abnormal Results of Laboratory Tests....58
8.5 Reporting and Follow–Up of Pregnancies....59
8.6 Adverse Events Leading to Discontinuation....60
8.7 Investigational Product Malfunction and Misuse....60
9 STUDY ACTIVITIES....61
9.1 Screening Visit (Day -31 to Day -4)....61
9.2 Admission (Day -3)....63
9.3 Investigational Period....65
9.3.1 Days of Smoking Abstinence (Day -2, Day -1 and Day 2)....65
9.3.2 Days of Single Use (Day 1 and Day 3)....66

9.4 Discharge 68
9.5 Safety Follow-up Period 69
9.6 Early Termination Procedures 70
10 QUALITY CONTROL AND QUALITY ASSURANCE....71
10.1 Monitoring 71
10.2 Training of Collaborators....71
10.3 Audits and Inspections....72
11 DATA MANAGEMENT ACTIVITIES....73
11.1 Data Capture 73
11.1.1 Case Report Forms and Study Records....73
11.1.2 Protocol Deviations....73
11.2 Data Handling....74
11.2.1 Data Verification....74
11.2.2 Coding....74
11.2.3 Database Lock....75
12 PLANNED STATISTICAL METHODS 76
12.1 General Considerations....76
12.1.1 Stratification Criteria....76
12.1.2 Definitions for Statistical Data Analysis....76
12.1.3 Descriptive Statistics....76
12.1.4 Handling of Missing Values and of Values outside the Detection Limits 76
12.1.5 Significance Level for Inferential Analysis 77
12.2 Determination of Sample Size and Power Consideration....77
12.3 Analysis Populations....77
12.3.1 PK Populations....77
12.3.2 Safety Population 77
12.4 Demographics and Baseline Characteristics....78
12.5 Primary Endpoints 78
12.5.1 Primary Endpoints Analysis Variables 78

12.5.2 Baseline Comparability 78
12.5.3 Descriptive Analysis 78
12.5.4 Confirmatory Analyses 79
12.6 Secondary Endpoints 79
12.6.1 Secondary Endpoint Analysis Variables 79
12.6.2 Baseline Comparability 79
12.6.3 Descriptive Analysis 80
12.6.4 Confirmatory Analyses 80
12.6.5 Safety Endpoints 80
12.7 Exploratory Analyses 81
12.8 Interim Analysis 81
13 ADMINISTRATIVE CONSIDERATIONS 82
13.1 Investigator's and Study Administrative Structure 82
13.1.1 Investigator 82
13.1.2 Sponsor 82
13.1.3 Other Responsibilities 83
13.2 Subject Confidentiality 83
13.3 Access to Source Documentation 84
13.4 Record Retention 84
13.5 Clinical Study Report 86
13.6 Financial Disclosure 86
13.7 Publication and Disclosure Policy 86
13.8 Insurance 86
14 REFERENCE LIST 87
15 APPENDICES 90
15.1 Appendix A – Schedule of Events 90
15.2 Appendix B - Participating Laboratories 94
15.3 Appendix C - Investigational Product and Instructions for Use 95
15.4 Appendix D - Abnormal Laboratory Values 96

LIST OF IN-TEXT TABLES

Table 1 Definition of Randomization Sequences 30
Table 2 Single Use of Products (Day 1 and Day 3) 40
Table 3 Description of Blinded Study Personnel 41
Table 4 Drugs and Substances Considered Interacting with CYP2A6 43
Table 5 Clinical Laboratory Parameters for Safety Panel 50
Table 6 Time Schedule – Screening (Day -31 to Day -4) 61
Table 7 Time Schedule – Admission (Day -3) 63
Table 8 Time Schedule – Wash-out (Day -2, Day -1) 65
Table 9 Time Schedule – Wash-out (Day 2) 66
Table 10 Time Schedule – Single Use (Day 1 and Day 3) 66
Table 11 Time Schedule – Day 4 Discharge 69
Table 12 Time Schedule – Early Termination Procedures 70
Table A1 Schedule of Events 90
Table D1 Abnormal Laboratory Values Rating: Serum Chemistry Parameters 96
Table D2 Abnormal Laboratory Values Rating: Hematology Parameters 97

LIST OF IN-TEXT FIGURES

Figure 1 Study Flow Chart 6
Figure 2 Study Flow Chart 29

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADL	Activities of daily living
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{(0-last)}$	Area under the concentration-time curve from T_0 to time of last quantifiable concentration
$AUC_{(0-t')}$	Partial AUC, where t' is the subject-specific time of maximum nicotine concentration following the single use of cigarettes
BMI	Body mass index
CC	Conventional cigarette(s)
CD	Compact disc
CI	Confidence interval
C_{last}	Last quantifiable concentration
C_{max}	Maximum concentration
CHTP	Carbon Heated Tobacco Product
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events and common toxicity criteria
CTMS	Clinical trial management system
CV (documentation)	Curriculum vitae
CV (statistics)	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
ECG	Electrocardiogram
EOS	End of study

FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
IxRS	Interactive web/voice response system
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
mCC	Menthol conventional cigarette
MCEQ	Modified cigarette evaluation questionnaire
MedDRA	Medical dictionary for regulatory activities
MRTP	Modified risk tobacco product
PK	Pharmacokinetic(s)
PMI	Philip Morris International
QC	Quality control
QSU-brief	Questionnaire of smoking urges
SAE	Serious adverse event
SAP	Statistical analysis plan
SHM	Sample handling manual
SOP	Standard operating procedure
T	Time point
T_0	Time point of first product use during study day

$t_{½}$	Half-life
t_{max}	Time to maximum concentration
[redacted]	[redacted]
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
WBC	White blood cell (count)
WHO	World Health Organization
λ_z	Terminal elimination rate constant

Explanation of Terms

The following special terms are used in this protocol:

End of Study	End of Study (EOS) is defined as the discharge on Day 4 or the date of early termination of the last subject plus a 7-day Safety Follow-up Period.
Enrolment	Enrolment is the period starting at the time of the first product test use at Admission until EOS.
First product use time point	Start of the product use of the CHTP 1.1 M or mCC corresponding to the first puffing of the CHTP 1.1 M or mCC.
mCC	The term 'menthol conventional cigarette' refers to manufactured and commercially available menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M)	CHTP 1.1 M is a tobacco stick which is comparable in shape and form, and is used in a similar manner to a menthol conventional cigarette. To use the CHTP 1.1 M, the consumer removes the protective cap and uses a conventional lighting method to ignite the heat source. [redacted], the aerosol generated by the heating process is inhaled by placing the lips on the filter and drawing air through the CHTP 1.1 M.
Randomization	Assignment to the respective product at any time on Day -1 utilizing an interactive web/voice response system (IxRS). On Day 1, the subjects will be individually informed about the product they are randomized to just before the first product use.

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

1 ETHICS AND REGULATIONS

1.1 Institutional Review Board Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] which includes both subject information sheet and informed consent, subject recruitment procedures [*e.g.*, advertisements], written information to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Investigator's curriculum vitae and/or other evidence of qualifications, the list of any other documents requested by the Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB. The IRB 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]), Ministerial Ordinance on GCP for drugs, and local legal and regulatory requirements, as applicable.

In accordance with GCP, a written confirmation of the IRB 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 IRB, with dates and version numbers, as well as the date of approval. The composition of the IRB, 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 IRB will be filed in the Investigator's file, and another original copy will be filed in the study master file (SMF) at the Sponsor or designated organization. The study must not start before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB.

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 IRB, and substantial amendments will only be implemented after approval by the IRB.

These requirements for approval should in no way prevent any action from being taken by the Investigator 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, and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately.

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

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 2013 [2] and are consistent with ICH/GCP [1], Ethical Guidelines for Clinical Studies (Ministry of Health, Labour and Welfare, 2003 [as last amended on July 31, 2008]) [3], Ministerial Ordinance on Good Clinical Practice for Drugs (as last amended by the Ordinance of Ministry of Health, Labour and Welfare) [4], and applicable regulatory principles and requirements.

The Investigator agrees to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IRB. 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 2013 [2] should be located in the Investigator's study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

At the Screening Visit, the Investigator will ensure 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 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 in the study, the subject and the person who conducted the inform consent discussion will both sign, date and time the ICF. The ICF includes both the subject information sheet and informed consent. No study-specific procedures will be performed before the ICF has been signed (including date and time).

The original, dated, and signed ICF(s) is kept in the Investigator study file at the site, and a copy must be given to the subject.

The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless the subject disagrees 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 Amendment to the Informed Consent Form

If a protocol amendment is required, or if any new information regarding the risk profile of the investigational product (IP) becomes available, or for any other reason deemed necessary, an amendment to the ICF may be required. 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 a relevant IRB before subjects are required to re-sign the ICF (including date and time). If new and important safety information is received, subjects who already completed or are discontinued from the study will be informed by letters, emails or phone calls.

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 the Investigator abide by the principles of the ICH guidelines on GCP [1]. These guidelines apply specifically to pharmaceutical development but nevertheless provide a robust and ethical framework for conducting clinical studies of tobacco 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 will carry out the clinical study in accordance with applicable national and local laws of the pertinent regulatory authorities.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

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. To those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases. These products are now referred to by the US Food and Drug Administration (FDA) as Modified Risk Tobacco Products (MRTPs) [5].

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

2.1.2 Description of the Product and Scientific Findings

Thousands of smoke constituents are formed when tobacco is burned or combusted. More than 6,000 of these smoke constituents have been identified [6], and more than 100 of them have been categorized as HPHCs [7].

The product developed by PMI, and to be assessed in this study, is the Carbon Heated Tobacco Product 1.1 Menthol (CHTP 1.1 M). CHTP 1.1 M avoids combustion and is heating tobacco to significantly lower temperatures than CC.

CHTP 1.1 M is a tobacco stick which looks the same as, and is used in a similar manner to a mCC. To use the CHTP 1.1 M, the consumer removes the protective cap and uses a conventional lighting method to ignite the heat source. [redacted], the aerosol generated by the heating process is inhaled by placing the lips on the filter and drawing air through the CHTP 1.1 M. During use, the tobacco in the CHTP 1.1 M is exposed to a well-defined temperature profile which ensures heating without combustion and at the same time provides an acceptable consumer experience in a consistent manner.

The non-clinical assessment of CHTP 1.1 M is described in the investigator's brochure and supports the clinical assessment of CHTP 1.1 M.

One clinical study has been conducted with CHTP 0.1, an earlier and non-menthol development version of the CHTP 1.1 M, in Europe. The study showed marked reductions in exposure to HPHCs compared to subjects continuing smoking CC in controlled conditions and no safety concerns. No clinical studies have been conducted with the CHTP 1.1 M.

2.2 Purpose of the Study

The purpose of this clinical study is to evaluate the profile of nicotine uptake (rate and extent of nicotine absorbed) after single use of the CHTP 1.1 M compared to mCC in healthy smokers.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Information on health risks associated with smoking and smoking cessation advice will be provided at Screening, at Admission, and at Discharge. The advice will follow the recommendations of the World Health Organization (WHO) [8] "Evidence based Recommendations on the Treatment of Tobacco Dependence". Subjects who are motivated to quit smoking during the study will be given the opportunity to continue their smoking cessation attempt and will be referred to appropriate stop smoking services for continuing support and counselling at a higher level. 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 with short-acting bronchodilator at Screening) per study protocol and scientifically accepted standards.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product (CHTP 1.1 M)

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

All risks related to study procedures and the product will be explained in detail to the subjects. Support for smoking abstinence will be provided. Further risk mitigation will include:

- Using commonly accepted research and scientific standards (*e.g.*, blood samples not to exceed blood donation standards).
- Management and follow-up of adverse events (AEs)/serious adverse events (SAEs).

- Medical assessment, management of all study participants with follow-up of those who have experienced an AE(s)/SAE(s).

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detailed to study participants. Unexpected malfunction of the CHTP 1.1 M may lead to unforeseeable risk. Subjects will be informed that the CHTP 1.1 M is not demonstrated to be less harmful than mCC. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoints

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

Endpoints:

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

3.2 Secondary Objectives and Endpoints

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

   Endpoints:

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

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

   Endpoint:

   - t_{max}

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

   Endpoint:

   - $t_{1/2}$

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

   Endpoint:

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

5. To describe product evaluation of the CHTP 1.1 M and mCC.
   Endpoint:
   - Product evaluation questionnaire (modified cigarette evaluation questionnaire [MCEQ]) subscales scores
6. To describe the levels of carbon monoxide (CO) exposure for the CHTP 1.1 M as compared to mCC.
   Endpoint:
   - CO exposure biomarkers: levels of exhaled CO and carboxyhemoglobin (COHb) in blood
7. To monitor the safety during the study.
   Endpoints:
   - Incidence of adverse events (AEs)/serious adverse events (SAEs)
   - Respiratory symptoms: cough assessment by visual analogue and Likert scales and one open question
   - Vital signs
   - Spirometry
   - Electrocardiogram (ECG)
   - Clinical chemistry, hematology, and urine analysis safety panel
   - Physical examination
   - Concomitant medication.
   - Incidence of CHTP 1.1 M malfunctions and misuse, [redacted]

Additional study assessments (for Baseline characteristics):

- Serology for human immunodeficiency virus 1/2 and hepatitis B and C
- Urine pregnancy test (female subjects of childbearing potential only), urine cotinine test, urine drug screen
- Alcohol breath test
- Chest X-ray
- Nicotine dependence to be assessed with the Fagerström test for nicotine dependence revised version

- Cytochrome P450 2A6 (CYP2A6) activity expressed as *trans*-3'-hydroxycotinine/cotinine molar metabolite ratio in plasma

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

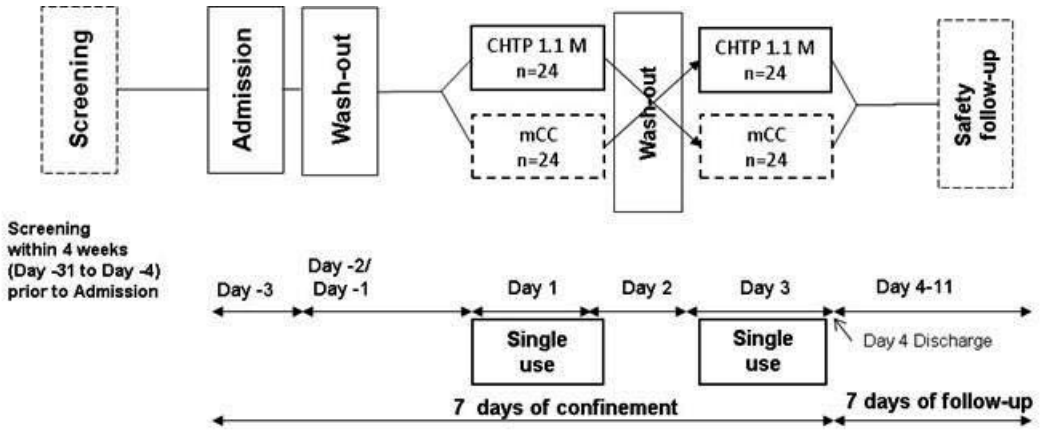
This is a randomized, controlled, 2-period, 2-sequence, single-use crossover study. Each subject will receive CHTP 1.1 M and mCC (Figure 2).

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

Subjects that terminate the study after Enrolment and prior to completion of the study will be asked to undertake early termination procedures (section 9.6).

1) Screening and Admission (from the ICF signature to the enrolment at Admission):

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



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

Figure 2 Study Flow Chart

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

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

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

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

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

Table 1 Definition of Randomization Sequences

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

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

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

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

A 7-day safety follow-up will be done for the recording of spontaneously reported AEs and SAEs (passive surveillance) and the active follow-up by the investigational site of AEs/SAEs ongoing at Discharge. Any AE will in general be followed-up until resolved, stabilized (*i.e.*, no worsening of the event), or until a plausible explanation for the event has been found.
The end of study for the subject is defined as the Discharge on Day 4 or the date of early termination of the subject plus a 7-day safety follow-up period. For further information on safety follow-up requirements refer to section 8.2.

4.2 Rationale for Study Design and Control Group

The minimum age of 23 years old in the inclusion criteria was selected based on:

- The legal age of smoking in Japan is 20 years
- To account for the 3 years of smoking history

In this study, mCCs (up to 1.0 mg nicotine ISO yield/mCC) will be used as a reference product.

The nicotine wash-out period was set to a minimum of approximately 48 hours (more than 5 times the half-life elimination of nicotine) as the half-life elimination ($t_{1/2}$) of nicotine in blood observed was about 4 hours in a previous study with the Tobacco Heating System 2.2 Menthol [9]. In a cross-over study, the washout period should be of the same duration for the two periods. Due to logistical reasons (smoking is difficult to be controlled by the site staff overnight), the wash-out prior to the first period will be slightly longer (approximately 57 hours) than the second period (approximately 48 hours).

The use of estrogen contraceptive is known to accelerate nicotine clearance by 20% - 30% in women as compared to women who do not take such [10]. Therefore, for the purpose of this study, it is not allowed to use hormonal contraception containing estrogens. This also applies to hormone replacement therapy.

The activity of CYP2A6 will be measured at baseline as nicotine metabolism by CYP2A6 varies between individuals of the same ethnicity/race and across ethnicity/race due to genetic variations. These genetic differences could be associated with reduced/increased nicotine metabolism [11].

4.3 Study Duration

The entire study per subject will last from 15 to 42 days, including a Screening period of up to 28 days (Day -31 to Day -4) prior to Admission, and 7 days of confinement (Day -3 to time discharge on Day 4). In the morning of Discharge (Day 4), examinations will be conducted. After Discharge, subjects will then enter a 7-day safety follow-up (until Day 11) for the recording of spontaneously reported AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site.

4.4 Appropriateness of Measurement

All laboratory measures utilized for this study are validated and are appropriate for the study assessments.

All questionnaires used in this study, except cough questionnaires, are available as validated questionnaires.

5 STUDY POPULATION

Forty-eight female or male Japanese currently smoking healthy adult subjects who smoke at least 10 mCC per day will be randomized into this study. The number of mCC consumption is not limited. Subjects must have a smoking history of at least 3 years of consecutive smoking prior to Screening. The smoking status of the subjects will be verified based on a urine cotinine test (cotinine ≥ 200 ng/mL).

Subject who signs informed consent form but does not meet the entry criteria prior to enrolment at Admission or met all entry criteria, but was not enrolled due to completion of enrolment (i.e., supernumerary subject) will be considered as screen failure.

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 at a minimum 23 years of age (inclusive).	Safety	X	
3. Subject is Japanese.	Administrative	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

Inclusion Criteria	Rationale	Screening	Admission (Day -3)
5. Subject smokes at least 10 commercially available mCCs per day (no brand restriction) with a maximum yield of 1 mg nicotine ISO/mCC, as labelled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject has been smoking for at least the last 3 consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	X
6. The subject does not plan to quit smoking in the next 3 months.	Safety	X	
7. The subject is ready to accept interruptions of smoking for up to 6 days.	Safety	X	X
8. The subject is ready to accept using the CHTP 1.1 M.	Effect		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's judgment, the subject cannot participate in the study for any reason (*e.g.*, medical, psychiatric, and/or social reason).	Safety	X	X
2. A subject who is legally incompetent, or physically or mentally incapable of giving consent (*e.g.*, emergency situation, under guardianship, prisoners, or subjects who are involuntarily incarcerated).	Administrative	X	

Exclusion Criteria	Rationale	Screening	Admission (Day -3)
3. The subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject).	Safety	X	X
4. The subject has $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted value at post-bronchodilator spirometry [12].	Safety	X	
5. The subject has asthma condition ($FEV_1/FVC < 0.75$ and reversibility in $FEV_1 > 12\%$ (or > 200 mL) from pre- to post-bronchodilator values).	Safety	X	
6. The subject has a body mass index (BMI) < 18.5 or ≥ 32.0 kg/m^2.	Safety	X	X
7. As per the Investigator's judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (*e.g.*, start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.	Effect	X	X
8. The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or nicotine replacement therapies), as well as electronic cigarettes and similar devices, within 4 weeks prior to Screening.	Effect	X	X

Exclusion Criteria	Rationale	Screening	Admission (Day -3)
9. The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer) which has an impact on CYP2A6 activity.	Effect		X
10. The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in study.	Administrative	X	X
11. The subject has a positive urine drug test.	Administrative	X	X
12. The subject has a positive serology test for HIV 1/2, hepatitis B, or hepatitis C.	Safety	X	
13. Donation or receipt of whole blood or blood products within 3 months prior to Admission.	Safety	X	X
14. The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).	Administrative	X	
15. The subject is an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, child).	Administrative	X	
16. The subject has participated in a clinical study within 3 months prior to the Screening Visit.	Safety	X	
17. The subject has been previously screened in this study and failed to meet the eligibility criteria.	Administrative	X	

Exclusion Criteria	Rationale	Screening	Admission (Day -3)
18. For women of childbearing potential only*: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission if not post-menauposal) or is breast feeding.	Safety	X	X
19. For women of childbearing potential only*: Subject does not agree to use an acceptable method of effective contraception.**	Safety	X	X

* Women who are not of childbearing potential meet at least one of the following criteria:

Have undergone hysterectomy or bilateral tubal ligation,

Have medically confirmed ovarian failure, or

Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

** Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-up Period. Hormonal contraception with estrogen containing products is NOT allowed in this study.

5.3 Discontinuation of Subjects from the Study

Discontinued subjects will include both, subjects who withdraw from the study (subject's decision) or subjects who are removed from the study. A subject can only be discontinued from the study after enrolment.

Subjects will be informed that they are free to withdraw from the study (upon decision of the subject) at any time. Subjects should be questioned for the reason for withdrawal from the study, although they are not obliged to disclose it. If the subject withdraws from the study he/she will be asked to confirm at least the following points and this information will be fully documented by Investigator:

- The subject agrees to undertake the early termination procedures (section 9.6) for safety assessments.

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, unless the subject disagrees in writing.

When a subject is discontinued from the study, all early termination procedures listed in section 9.6 are performed unless the subject refuses to perform the assessments. After the date of termination, the subject will enter into the 7-day safety follow-up period.

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

- Withdrawal of informed consent.
- Any AE or condition (including clinically significant changes in a laboratory parameter) which at the discretion of the Investigator no longer justifies the subject's participation in this study.
- Positive pregnancy testing (section 8.5).
- The Sponsor or Investigator terminates the study or the study terminates at a particular site. If the Sponsor or the Investigator decides to prematurely terminate the study, the subject will be promptly informed. The head of the medical institution should report the fact and the reason in writing to the IRB.
- Discontinuation is considered to be in the best interest of the subject or the other subjects as judged by the Investigator.
- Subjects using any nicotine/tobacco product different from the assigned product will be withdrawn from the study.
- Subjects who do not meet inclusion #8 or any other eligibility criteria.
- Subject is not willing to use CHTP 1.1M after product test at Admission.

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

- Non-compliance to the study procedures based on the judgment of the Investigator.
- Sufficient number of subjects are already randomized to the study sequences[1].

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

5.4 Lost to follow up

The end of the study date for a subject lost to follow-up will be defined as the date when the Investigator decides that the subject is lost to follow-up, not to exceed the maximum duration of the study. A 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.

5.5 Violation of Selection Criteria

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

[1] Surnumerous (« back-up ») subjects should be discontinued from enrollement prior to randomization only.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

CHTP 1.1 M

CHTP 1.1 M is a tobacco stick which is comparable in shape and form, and is used in a similar manner to mCC. To use the CHTP 1.1 M, the consumer removes the protective cap and uses a conventional lighting method to ignite the Heat Source. [redacted], the aerosol is generated by drawing air through the CHTP 1.1 M. During use, the tobacco in the CHTP 1.1 M 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.

The CHTP 1.1 M will be provided by the Sponsor and its distribution will be limited to a qualified and appropriately trained study site collaborator. Additional information are provided in section 2.1.2.

The overall objective of the design CHTP 1.1 M is to provide an acceptable experience in which the HPHC level in the aerosol is substantially reduced in comparison with mCCs.

mCC

In the study sequences 1 and 2, the reference product to CHTP 1.1 M is commercially available single brand mCC. mCC will not be provided by the Sponsor. All eligible subjects will be asked to purchase their own preferred single-brand of mCC prior to Admission. Every study subject needs to buy his/her anticipated amount of single-brand mCC for a total of 2 days plus 2 extra packs.

6.2 Packaging and Labeling

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

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

Packs of mCC will be labeled to identify necessary information to match the subject with his/her suppliers.

For the CHTP 1.1 M, the packs will be printed with the necessary information including, but not limited to, product code and expiry date.

6.3 Use of Investigational Products

Subjects will never be requested or forced to smoke and will be free to stop smoking at any time of the 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).

6.3.1 Admission (Day -3)

Subject will be instructed not to smoke in the morning prior to Admission on Day -3. After Admission, smoking will not be allowed until blood drawing for the assessment of CYP2A6 activity and spirometry have been conducted. After these assessment procedures, smoking will be allowed until 11.00 PM of the Admission Day. All subjects (except women with a positive pregnancy test at Screening or Admission) will undergo a CHTP 1.1 M test.

6.3.2 Investigational Period (Day -2 to Day 3)

During the first wash-out, each subject will maintain smoking abstinence from Day -3 11:00 PM to the time of single use of his/her allocated product at Day 1. At Day 1, after the single use of the product, subjects will maintain smoking abstinence for the rest of the day. During Day 2, subjects will maintain smoking abstinence until the time of single use of his/her allocated product at Day 3. Subjects will not be allowed to smoke or use any other nicotine/tobacco-containing products other than the products they are allocated to.

Time point 0 (T_0) will be defined as start of the single product use on the single use days or as start of the first product use on each study day. The start time of product use for mCC and CHTP 1.1 M corresponds to the first puff of the mCC or CHTP 1.1 M. [redacted]

As randomization will take place at any time on Day -1, the subjects will be individually informed about the sequence they are randomized to just before the first product use on Day 1.

6.3.3 Single Use of Products (Day 1 and Day 3)

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

At Day 1, subjects randomized to sequence 1 will use one CHTP 1.1 M, subjects randomized to sequence 2 will smoke one mCC as shown in Table 2:

Table 2 Single Use of Products (Day 1 and Day 3)

	Sequence 1	Sequence 2
Day 1	CHTP 1.1 M	mCC
Day 3	mCC	CHTP 1.1 M

6.3.4 Day of Discharge

On the Day of Discharge (Day 4), smoking will be only allowed after all laboratory procedures and the spirometry have been performed. All examinations at Discharge will be conducted on Day 4 prior to Discharge.

6.3.5 Safety Period

During the Safety Follow-up Period, subjects are free to smoke according to their usual smoking habits.

6.3.6 Stopping Rules for Investigational Product

For safety purposes, using CHTP 1.1 M or smoking mCC 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. If the study product is discontinued, the reasons for discontinuation will be documented in the source documents and subjects will undertake early termination procedures (section 9.6).

6.4 Method for Assigning Subjects to Sequences

Randomization to product exposure sequence will be done through IxRS.

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

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

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

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

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

6.5 Blinding

This is an open-label study; therefore the subjects and Investigators will be unblinded to the subject's sequence. However, there will be a limited degree of blinding in the data review and data analysis process. In particular, PMI and CRO personnel will be blinded to the randomized sequence as summarized in Table 3:

Table 3 Description of Blinded Study Personnel

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

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

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

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

6.6 Investigational Product Accountability and Compliance

6.6.1 Dispensing Investigational Product

At Admission, on Day 1 and Day 3, the CHTP 1.1 M and mCC will be dispensed by the study site collaborator. Each dispense of the product to the subject will be recorded. In addition, the start times of using any product must be recorded for Day -3, Day 1 and Day 3.

The CHTP 1.1 M will not be promoted for commercial distribution or test market.

6.6.2 Storage and Accountability

The CHTP 1.1 M and mCC will be stored in a secured site storage place with limited access to the authorized personnel only. The study collaborator (the IP product storage manager) designated by the Head of the investigational site will be responsible for the storage and accountability of the IPs in accordance to sponsor's requirements.

Subjects will return each butt of any used CHTPs 1.1 M or mCC immediately after use to the site collaborators for accountability. The time of return of the products will be documented in an appropriate log. At the end of the study, unused mCCs given to the site collaborators at Admission will be given back to the subjects.

6.6.3 Investigational Product Retention

Unused CHTP 1.1 M will be destroyed or returned to the Sponsor upon study completion.

6.6.4 Compliance to Investigational Products

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

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

6.7 Restrictions

6.7.1 Smoking Restrictions

At the Screening Visit pre- and post-bronchodilator spirometry will be done at least 1 hour of not smoking.

Subjects will be instructed to abstain from smoking in the morning of the Admission (Day -3) until blood drawing for CYP2A6 activity assessment and spirometry will have been performed. Subjects will not have free access to their mCC which will be dispensed by the site collaborators individually as described in Section 6.6.1.

On Day 1 and Day 3, to avoid nicotine cross contamination, CHTP 1.1 M users and mCC smokers will use and smoke in dedicated separate rooms: one room for CHTP 1.1 M and one room for mCC. Every subject must use or smoke alone with an interval between subjects allowing ventilation of the room.

Using CHTP 1.1 M or smoking mCC is not allowed during study procedures except during blood sampling for nicotine PK on Day 1 and Day 3. Furthermore, smoking is not allowed at Discharge until the spirometry and all the laboratory procedures have been conducted.

During the days of wash-out or single product use, no NRT, nicotine-containing products or other products supportive to smoking abstinence are allowed to be used or will be provided to the subjects.

6.7.2 Dietary Restrictions

A standard diet will be designed by a dietician for the whole confinement period. For each meal, the caloric and fat content should be controlled in order to avoid a “high-fat” diet. A “high-fat” diet is defined as a diet which contains “approximately 50 percent of total caloric content of the meal (from fat) and is high in calories (approximately 800 to 1000 calories)” [13].

Subjects are not allowed to bring their own food or beverages to the investigational site. Meals will be served according to the schedules provided in section 9. 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 water is allowed as desired. Consumption of quinine-containing drinks (*e.g.*, tonic water) is not allowed. The same menu and meal schedule will be administered uniformly for all subjects in all sequences.

Fasting state has to be observed for at least 10 hours prior to blood drawings for the safety laboratory at Admission and at Discharge.

6.7.3 Concomitant Medication

For the purpose of this study, no concomitant medication should be taken by the subjects from screening to Discharge without prior informing the Investigator or designee. Any medication with an impact on the CYP2A6 metabolism (as prescription and over-the-counter products) as presented below in Table 4 must be avoided.

In this study, it is not allowed to use hormonal contraception containing estrogens. This also applies to hormone replacement therapy. Hormonal contraception with products containing progesterone only is allowed during this study. Subjects using estrogens during the study will be withdrawn.

The following drugs and substances are examples considered as having an impact on CYP2A6 activity ([14], Table 4). Prior to database closure, the concomitant medication will be assessed according to the potential impact on CYP2A6 activity and the potential impact on study results.

Table 4 Drugs and Substances Considered Interacting with CYP2A6

Inhibitor	**Drug Class**
Amiodarone	Antiarrhythmic agent
Desipramine	Antidepressant
Isoniazid	Antitubercular agent
Ketoconazole	Antifungal agent
Letrozole	Antineoplastic agent
Methoxsalen	Systemic psoralen
Miconazole	Antifungal agent
Tranylcypromine	Antidepressant
Inducer	**Drug Class**
Amobarbital	Barbiturate
Pentobarbital	Anticonvulsant, Barbiturate
Phenobarbital	Anticonvulsant, Barbiturate
Rifampin	Antibiotic, antitubercular agent
Secobarbital	Barbiturate
Substrate	**Drug Class**
Dexmedetomidine	α_2-Adrenergic agonist, sedative

Ifosfamide	Antineoplastic agent, alkylating agent

Data source: [14]. This list is not exhaustive.

The Investigator is responsible for the medical care of the subjects during their participation in this study. Any decision regarding the prescription of medication or over the counter medication will be taken in the best interest of the subject.

If the use of a concomitant medication cannot be avoided for the subject's safety, it has to be fully documented (section 7.4.5). Concomitant medications should be followed up with the CRO Medical Monitor on an ongoing basis.

Concomitant medication will be assessed at the Screening Visit. To be eligible for the study, any medication with impact on CYP2A6 metabolism must be discontinued at least 14 days prior to Admission to the clinic or for at least the duration that would be equal to five half-lives of the given substance (whichever is longer). They must not be used during the entire study until Discharge. It is at the discretion of the Investigator to assess if a termination of such medication at Screening is medically justified and safe for the subject.

6.7.4 Other

From Admission to Discharge, practice of intensive exercise and physical work-out will be prohibited as it may impact the nicotine absorption profile.

7 STUDY PROCEDURES

Personnel performing or recording study measurements must have the appropriate and fully documented training. Quality control (QC) measures have to be in place. All study procedures are provided as an overview in the schedule of events (section 15.1, Appendix A – Schedule of Events).

In this section, only the expected/planned time points for the various measurements are given. Considering that not all subjects can have a procedure at the same time point, adequate time windows are given for each study procedure and each time point in section 9. Site personnel will adhere to the site's standard operating procedures (SOPs) for all activities relevant to the quality of the study. Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

7.1 Informed Consent Form

Each subject must give his/her informed consent prior to participating in the study. During the consent process, the Investigator obtaining consent must inform each subject of the nature, risks and benefits of, and alternatives to study participation. In addition, each subject must review the ICF and must have sufficient time to understand and have adequate opportunity to ask questions. The ICF must be signed and dated (date and time) prior to undertaking any study-specific procedures. Once the ICF is signed the subject is part of the study and will not be allowed to re-enter in case of a screening failure due to an eligibility criteria not met or an early discontinuation. A copy of the signed ICF must be given to the subject.

7.2 Smoking Cessation Advice and Debriefing

Each subject will be given advice on the risks of smoking, with smoking cessation (SC) advice, three times during the study: at the Screening Visit, at Admission, and at Discharge. The form of a brief interview will be used according to current WHO recommendations [8]. Details of the interview will be recorded in the source document file. Information on the risk of smoking/smoking cessation advice will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the Investigator and may additionally be given in a group session.

In addition to the information of the risk of smoking/SC advice, a debriefing of subjects will be done at each smoking cessation advice session to address any intended or unintended beliefs participants have about CHTP 1.1 M. 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 1.1 M has not been demonstrated to be less harmful than mCC.

7.3 Support during Smoking Abstinence/Periods of Reduced Smoking

All subjects will be closely monitored by the site collaborators. This includes monitoring of clinical tests *e.g.*, vital signs, physical examination, and body weight. It also refers to close monitoring of the subject's behavior, AEs, and his/her mood.

7.4 Clinical Assessments

Any clinically significant finding detected during the Screening Visit has to be documented as a concomitant disease. This also applies to clinically significant findings in laboratory values, vital signs, and ECGs, detected during the Screening Visit. Any untoward medical occurrence in a subject detected during the study which was not present at the Screening Visit must be documented as an AE. Worsening of a pre-existing condition from the Screening Visit onwards will also be documented as an AE. If a clinically significant finding is detected during the screening period, the Investigator needs to check if exclusion criterion number 3 is still fulfilled.

7.4.1 Demographic Data

Demographic data (gender, date of birth/age) will be recorded at the Screening Visit.

7.4.2 Identification of the Current Cigarette Brand

Identification of the current mCC 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 mCC brand to the site and will have to hand their mCC supply for the confinement period to the site collaborators, who will take a photograph of the front and of the side of the cigarette pack supplied by the subject to document brand name and yields. Photos will be considered as source documentation. A copy of the photos will be provided to the Sponsor electronically as DVD or CD.

7.4.3 Smoking History and Willingness to Quit Smoking

Subjects will be questioned for their smoking history at Screening. This will include questions to evaluate whether the subject was a smoker for at least the last three consecutive years and to determine the number of mCC smoked during the previous 4 weeks. The subject will also be asked if he/she is planning to quit smoking during the next 3 months. In addition, the subject will be asked if he/she has used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT), electronic cigarettes, or similar devices, within 4 weeks prior to assessment.

Furthermore, subjects will be asked at Screening and Admission if they are ready for up to 6 days of smoking interruption. Only subjects prepared and able to comply with this requirement will be considered for participation in the study.

7.4.4 Demonstration and CHTP 1.1 M Test

All subjects will have a demonstration of the CHTP 1.1 M at the Screening Visit. Only subjects willing and ready to use the CHTP 1.1 M will be enrolled in the study. On Day -3, after enrolment, subjects will have a product test, using 3 to 5 CHTP 1.1 M.

7.4.5 Medical History, Concomitant Disease, Previous and Ongoing Medications

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

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

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

7.4.6 Physical Examination

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

7.4.7 Body Height and Weight

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

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

7.4.8 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured at the Screening Visit, at Admission, at every day in confinement, and at Discharge. All parameters will be recorded in supine position after the subject has rested for at least 5 minutes.

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

7.4.9 Other Clinical Assessments

7.4.9.1 Spirometry

Spirometry with and without a short-acting bronchodilator (*i.e.,* pre- and post-bronchodilatator) will be done at the Screening Visit to evaluate inclusion/exclusion criteria. At Screening, spirometry pre- will be done first, followed by spirometry post-bronchodilator. Spirometry pre- and post- bronchodilator at Screening will be used for eligibility. Furthermore, spirometry pre-bronchodilator will be performed at Admission prior to product test as well as at Discharge. See section 6.7.1 for the smoking restrictions associated spirometry.

Spirometry will follow the 2005 testing and quality recommendations by the American Thoracic Society/European Respiratory Society Joint Task Force on the standardization of spirometry along with the electronic data submission and documentation processes [15]. Spirometry predicted values will be standardized to the Japanese Respiratory Predicted set [16].

All personnel performing lung function testing should have the appropriate training and QC measures should be put into place and be properly documented and filed at the pulmonary function laboratory (including the records of the calibration, if applicable). The FEV_1, FVC, and FEV_1/FVC will be recorded.

7.4.9.2 Electrocardiogram

An ECG will be recorded at Screening and on the following study days: Day 1 and Day 3 (single use days). The ECG testing will be performed as per the site local practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected by the ECG device according to Bazett's formula. Every ECG has to be assessed as normal, abnormal – clinically not significant, or abnormal – clinically significant. A diagnosis has to be provided in the CRF for all ECGs assessed as abnormal – clinically significant. ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied, initialed, dated, and stapled together for inclusion in the source data file.

7.4.9.3 Chest X-ray

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

7.5 Biomarker Assessment

All bioanalytical assays and laboratory assessments (section 7.6) will be carried out using validated methods. The bioanalytical methods used will be documented in the bioanalytical plans and the results reported in the bioanalytical reports. A list of laboratories is provided in section 15.2.

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

7.5.1 Biomarker of Exposure

7.5.1.1 Biomarker of Exposure to CO and COHb

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

CO Breath Test

CO in exhaled breath will be measured using the Smokerlyzer® device such as Micro+™ Smokerlyzer® device or similar.

A CO breath test will be conducted once at Day -3 and Day 4.

On Day -2, Day -1, Day 1, Day 2, and Day 3, four CO breath tests will be done per day. On Day 1 and Day 3, the first test per day will be performed within 15 minutes prior to T_0. The three other tests will be conducted as described in section 9.

COHb Test

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

7.5.1.2 Biomarkers of Exposure to Nicotine

Blood samples to measure nicotine in plasma will be taken as follows:

Single-Use Day 1 and Day 3 for mCC and CHTP 1.1 M:

A total of 16 blood samples will be taken for a 24-hour profile. The first blood sample will be taken within 15 minutes prior to the single use (Day 1 and Day 3, T_0). Times of sampling are thereafter in relation to T_0: T_1 after 2 minutes, T_2 after 4 minutes, T_3 after 6 minutes, T_4 after 8 minutes, T_5 after 10 minutes, T_6 after 15 minutes, T_7 after 30 minutes, T_8 after 45 minutes, T_9 after 60 minutes, T_{10} after 2 hours, T_{11} after 4 hours, T_{12} after 6 hours, T_{13} after 9 hours, T_{14} after 12 hours, and T_{15} after 24 hours (this sample will be drawn during the day following product use, *i.e.*, wash-out).

7.5.2 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Day -3. CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites. In this study the CYP2A6 activity will be measured using the metabolic molar ratio of *trans*-3'-hydroxycotinine/cotinine.

7.6 Laboratory Assessments

A list of laboratories is provided in section 15.2.

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

Hematology, clinical chemistry, and urine analysis for the safety panel will be measured at Screening, at Admission and at Discharge. Tests will be conducted at a local laboratory or the site. Blood will be taken after no less than the 10 hours of fasting at Admission and Discharge (section 6.7.2). Samples at screening will be taken in a non-fasting status. The urine test will be performed semi-quantitatively as urine dip-stick test at a local laboratory or the site. Parameters to be measured are listed in Table 5.

Table 5 Clinical Laboratory Parameters for Safety Panel

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
	- Glucose
	- Lactate dehydrogenase
	- Potassium
	- Sodium
	- Total bilirubin
	- Direct bilirubin
	- Total cholesterol
	- Triglycerides
		- pH
		- Bilirubin
		- Glucose
		- Nitrite
		- Red blood cell traces
		- Protein
		- Specific gravity

7.6.2 Serology

A test for hepatitis B surface antigen, hepatitis C virus, and HIV (anti-HIV 1/2 and p24 antigen) will be done at the Screening Visit. In case of positive results, the subject will be referred to appropriate medical care.

7.6.3 Urine Drug Screen

A urine drug screen will be performed at the site at the Screening Visit and on the Day of Admission. The urine will be screened for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

7.6.4 Urine Cotinine Screening

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

7.6.5 Alcohol Breath Test

Subjects will undertake a breath alcohol test at the Screening Visit and at Admission to the clinic using an alcometer device.

7.6.6 Urine Pregnancy Testing

All female subjects of childbearing potential will have pregnancy testing at the Screening Visit, at Admission to the clinic, and at Discharge. In any case of a positive pregnancy test, the Investigator will inform the subject about the risks associated with smoking during pregnancy.

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

7.7 Sample Handling, Storage, and Shipment

Participating laboratories for blood samples testing will be decided prior to the Investigator meeting and site initiation. Safety laboratory samples will be tested at a local laboratory or site (section 15.2).

Detailed procedures for handling of samples are described in the separate sample handling manual (SHM). Safety laboratory samples will be destroyed as by the laboratories standard procedures. All other samples will be destroyed post database lock or post finalization of the bioanalytical reports depending which one is coming the latest. The facility/-ies at which the samples are stored will be informed in writing by the Sponsor when destruction of the samples shall be performed.

7.7.1 Blood Samples

Blood samples will be drawn by qualified and trained site personnel. Subjects should be in a seated position during blood collection. In total, around 210 mL will be drawn for this study

including planned assessments, safety, and repeated analysis for safety. This is comparable to a standard blood draw for donation. The required aliquots and volumes for assessments of blood/plasma parameters and tests are summarized in the SHM.

7.7.2 Urine Samples

Spot urine samples will be taken for urine drug screen, cotinine screen, pregnancy tests, and safety urinalysis.

7.8 Questionnaires

The subject questionnaires and the visual analogue scale (VAS) will be entered by the subject directly in the electronic patient reported outcomes device or in paper copy. The questionnaires will be reviewed for completeness by the study site collaborators and subjects will be requested to complete any missing information.

7.8.1 Fagerström Test for Nicotine Dependence (FTND, revised version)

Potential nicotine dependence will be assessed at Screening using the FTND in its revised version [17] as updated in 2012 [18].

The questionnaire consists of six questions which have to be answered by the subject himself/herself. The scores obtained on the test permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) [18].

7.8.2 Assessment of Cough

Subjects will be asked if they have experienced a regular need to cough, *e.g.*, coughing several times in the last 24 hours prior to assessment. If the answer is 'yes', they will be asked to complete a VAS, three Likert scales, and an open question also assessing the previous 24 hours.

The VAS will assess how bothersome cough is to the subject ranging from 'not bothering me at all' to 'extremely bothersome'.

Furthermore, subjects will be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales:

- The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = very mild – 2 = mild – 3 = moderate – 4 = severe – 5 = very severe
- The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = rarely – 2 = sometimes – 3 = fairly often – 4 = often – 5 = almost always
- The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3, with 0 = no sputum – 1 = a moderate amount of sputum – 2 = a larger amount of sputum – 3 = a very large amount of sputum

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

Assessments will be done on a daily basis on Day -2 and from Day 1 to Day 4. On Day 2 and Day 4, questionnaire must be asked 24 hours after T_0 of Day 1 and 24 hours after T_0 of Day 3.

7.8.3 Modified Cigarette Evaluation Questionnaire (MCEQ, modified version)

Product evaluation will be assessed using the MCEQ [19]. 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).

This questionnaire will only be completed by the subjects, who use the CHTP 1.1 M or smoke mCCs during the study. The MCEQ will be completed by subjects themselves on Day 1 and Day 3.

7.8.4 Questionnaire of Smoking Urges

To assess the urge-to-smoke, all subjects will be asked to complete a 10-item brief version of the QSU [20]. The QSU-brief is a 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 [21]. The findings supported a multi-dimensional conceptualization of craving to smoke and demonstrated the utility of a brief multi-dimensional measure of craving [20].

The QSU-brief will be completed by the subject himself/herself at single use study days in all subjects.

The first assessment will be made within 15 min prior to T_0, 9 assessments thereafter in relation to T_0: 15 minutes, 30 minutes, 45 minutes, 60 minutes, 2 hours, 4 hours, 6 hours, 9 hours, and 12 hours after T_0.

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 [22]), an AE is defined as any untoward medical occurrence in a subject administered an IP or reference product, which does not necessarily have a causal relationship with the IP or reference product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP or reference product, whether or not it is considered related to the IP or reference product.

8.1.2 Serious Adverse Events

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

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

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

Any pre-planned hospitalizations that are known at the time of signing the ICF/subject information sheet will not be recorded as SAEs, however they will be recorded as AE only. Any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

8.2 Assessment of Adverse Events

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

8.2.1 Collection of Information

Adverse event information will be collected from the time of signature of the ICF onwards until the EOS either by the Investigator via spontaneous reporting or by the use of consistent, open, non-directive questions from study site collaborators (*e.g.*, “Have you had any health problems since the previous visit/How have you been feeling since you were last asked?”). At

the discretion of the Investigator or designee, the collection of AE information may also be triggered from his/her review of the subject questionnaires and the VAS. However, the main source for AE collection will be face-to-face interview(s) with the subject.

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

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

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

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

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

8.2.2 Period of Collection

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

8.2.2.1 Screening Period

All existing health conditions identified during the Screening period starting at the time of ICF signature and judged by the Investigator as preexisting condition will be recorded as concomitant disease and the subject's eligibility for admission to the study will be reviewed.

Any AEs which occur during the Screening Period will be captured by the site collaborators and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study procedures. All collected AEs will be reported in the CSR and will be in accordance with the respective regulatory guidelines.

8.2.2.2 Admission until End of Study

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

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

During the safety follow-up period AEs and/or SAEs will be recorded after spontaneous reporting by the subject. SAEs will be reported by the Investigator as described in this

document and the safety management plan (SMP). Any ongoing AEs/SAEs during the safety follow-up period will be actively followed up by the site until they have been resolved, stabilized (*i.e.*, no worsening of condition), or an acceptable explanation has been found.

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

8.2.3 Intensity of Adverse Event

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

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

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

Severe: The AE is incapacitating and requires medical intervention.

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

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

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

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

8.2.5 Expectedness

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

8.3 Reporting and Follow-Up of Serious Adverse Events

Any SAEs reported or observed during the study whether or not attributable to the IP, or to any study procedures, or any SAE related to the product and spontaneously reported after the safety follow-up must be reported by the Investigator **within 24 hours after first awareness by any party involved in the study** to [redacted] and to the Sponsor.

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

[redacted]:	**Fax number:**	[redacted]
	E-mail:	[redacted]
	Address:	[redacted]

1 May – 31 May 2015 Interim Period

Sponsor: Contact: [redacted], MD, Medical Safety Officer	**Phone number:**	[redacted]
	E-mail:	[redacted]
	Address:	Philip Morris Products S.A. R&D Innovation Cube T3551 Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

From 1st June 2015 onwards

Sponsor: Contact: [redacted], MD, PhD, MFPM, Medical Safety Officer	**Phone number:**	[redacted]
	E-mail:	[redacted]
	Address:	[redacted]

The Investigator/head of the investigational site is responsible for local reporting (*i.e.*, to the IRB) of SAEs that occur during the study, according to local regulations.

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

The follow-up SAE report form must include the minimum information required 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.

All SAEs will be followed up by the Investigator until their resolution or until the Investigator considers the event to be stabilized (*i.e.*, no worsening of condition), or until an acceptable explanation has been found (*e.g.*, a chronic condition). The details of the SAE management will be provided in a separate document which is included in the safety management plan (SMP).

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

8.4 Reporting of Other Events Critical to Safety Evaluations

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for clinical significance. If the Investigator considers the abnormal result to be clinically significant, then it must be recorded as a concomitant disease at Screening, or if not present at Screening, as an AE during the study.

The grading scheme shown in section 15.4 will be used by the Investigator to assess abnormal laboratory AEs as follows:

- All Grade 1 abnormal laboratory values will be evaluated by the Investigator with respect to Baseline value and clinical significance. If considered to be clinically significant, the Investigator must report it as an AE. All Grade 2 and higher abnormal laboratory values must be reported as or linked to an AE/concomitant disease.
- If a subject has Grade 2 and higher abnormal laboratory values at Screening it is at the discretion of the Investigator to enroll the subject or not. This decision must be documented in the source documentation and captured in the CRF. A grade 2 laboratory abnormal value at the Screening Visit must be recorded as concomitant disease.
- If there is any worsening in grade from Grade 2 and above during the study, the Investigator must report this worsening as an AE.

- Where there is no grading available, the abnormal laboratory value will be evaluated by the Investigator and assessed for clinical significance. If considered to be clinically significant, the Investigator will report it as an AE.
- Any other abnormal clinical laboratory result (including those that are not part of the core safety assessments) can, at the discretion of the Investigator, be reviewed and assessed. Even if they do not meet the criteria of the CTCAE grading scheme (please see above), the Investigator may consider them to be of clinical significance and, if they are, must report them as AEs.
- In general, laboratory values will be recorded as 'increased <lab parameter>' or 'decreased <lab parameter>' to ensure consistency of recording/coding.

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

8.5 Reporting and Follow–Up of Pregnancies

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

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

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

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

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

[redacted] will follow up pregnancies only if they were detected after first product use (*i.e.*, after CHTP 1.1 M test at Admission). If pregnancies are to be followed-up, they will be followed-up until an outcome is reached (*e.g.*, normal delivery, spontaneous abortion, or voluntary termination). Any pregnancy complication, adverse pregnancy outcome, or maternal complications will be recorded.

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

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the EOS procedures, as described for Discharge, as soon as possible and will enter the period of safety follow-up. The Investigator will follow up these AEs until they have been resolved, stabilized (*i.e.*, no worsening of condition), or an acceptable explanation has been found.

8.7 Investigational Product Malfunction and Misuse

Any occurrences of the CHTP 1.1 M malfunction [redacted] or misuse (use not in accordance with its label and instruction) by a subject will be documented by the Investigator or his/her designated collaborator using a product quality complaint form.

Investigational product misuse may result in use-related hazards.

Furthermore, any misuse or malfunction of the CHTP 1.1 M that lead to an AE/SAE will follow the same processes as described above for the reporting of the AE/SAE.

9 STUDY ACTIVITIES

A detailed schedule of assessments can be found in Appendix A – Schedule of Events (section 15.1). 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 is implemented for subsequent subjects. Measurements not conducted at the exact time point, but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given time point.

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

9.1 Screening Visit (Day -31 to Day -4)

The Screening Visit will be performed within 4 weeks (Day -31 to Day -4) prior to Admission on Day -3.

The following assessments will be performed at the Screening Visit (the sequence of the assessment will be at the discretion of the site but all of them must be done after signature of the ICF):

Table 6 Time Schedule – Screening (Day -31 to Day -4)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Informed consent	
		Information on the risks of smoking, smoking cessation advice and debriefing	
		Demographic data	
		Smoking history	
		Identification of current mCC brand	
		Willingness to quit smoking in the next 3 months	
		Readiness to accept interruptions of smoking for up to 6 days	
		FTND questionnaire	
		Prior medication (4 weeks prior to Screening Visit)/concomitant medication	
		Medical history/concomitant diseases	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Vital Signs (pulse rate, systolic and diastolic blood pressure, respiratory rate)	At least 5 min in supine position prior to measurement. For every measurement, it has to be ensured and documented that the duration between the end of last smoking and the measurement should be at least 15 minutes.
		Height, weight, including calculated BMI	
	√	Clinical laboratory parameters (hematology, clinical chemistry)	
	√	Serology for HIV and Hepatitis B and C	
		Safety urine analysis	
		Urine drug screen	
		Alcohol breath test	
		Urine pregnancy test	For all female subjects of childbearing potential
		CHTP 1.1 M product demonstration	
		Spirometry pre- and post-bronchodilatator	Has to be done at least 1 hour of not smoking At rest 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
		ECG	At least 10 min in supine position prior to recording.
		Chest X-ray	If not performed 6 months prior to Screening
		AE/SAE questioning	If the Screening Visit is performed on two separate days the AE/SAE questions will be asked again.
		Physical examination	
		Urine cotinine screen test	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Inclusion/exclusion criteria	

Abbreviations: AE = adverse event; BMI = body mass index; mCC = menthol conventional cigarette(s); ECG = electrocardiogram; CHTP 1.1 M = Carbon Heated Tobacco Product 1.1 Menthol; FTND = Fagerström test for nicotine dependence (revised version); HIV = human immunodeficiency virus; SAE = serious adverse event.

9.2 Admission (Day -3)

The following assessments will be performed at Admission (Day -3):

Table 7 Time Schedule – Admission (Day -3)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Start of the Day		AE/SAE recording	All day
		Concomitant medication	All day
		Smoking abstinence	In the morning until blood drawing for CYP2A6 activity assessment and spirometry will be performed and after 11.00 PM.
		Information on the risks of smoking/smoking cessation advice and debriefing	
		Readiness to accept interruptions of smoking for up to 6 days	
		Readiness to use the CHTP 1.1 M	
	√	*trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma	Must be done prior to smoking.
		Spirometry	Has to be done prior smoking. At rest for at least 15 minutes prior to spirometry. In sitting position.
		Urine pregnancy test	For all female subjects of childbearing potential

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
	√	Clinical laboratory parameters (hematology, clinical chemistry)	In at least 10 hours of fasting.
		Safety urine analysis	
		Urine cotinine screen test	
		Urine drug screen	
Prior to 10:00 AM		Breakfast	
Prior to 11:30 AM		Vital Signs	At least 5 min in supine position prior to measurement. For every measurement, it has to be ensured and documented that the duration between the end of last smoking and the measurement should be at least 15 minutes.
Prior to 11:30 AM		Physical examination, weight and calculated BMI	
Prior to 11:30 AM		Identification of current mCC brand	
Prior to 11:30 AM		Alcohol breath test	
Prior to 11:30 AM		CO breath test	
Prior to 2:30 PM		Lunch	
Afternoon		Snacks	
		Inclusion/exclusion criteria	All eligibility criteria must be checked.
		Enrolment	
		Product test for CHTP 1.1 M	Use of 3 to 5 CHTPs 1.1 M
		Collection of used CHTP 1.1 M and mCC butts	
In the evening prior to 9:00 PM		Dinner	

Abbreviations: AE = adverse event; BMI = body mass index; mCC = menthol conventional cigarette(s); CHTP 1.1 M= Carbon Heated Tobacco Product 1.1 Menthol; CO = carbon monoxide; CYP2A6 = cytochrome P450 2A6; SAE = serious adverse event.

9.3 Investigational Period

9.3.1 Days of Smoking Abstinence (Day -2, Day -1 and Day 2)

On the days of smoking abstinence (Day -2, Day -1 and Day 2) the following assessments will be performed:

Table 8 Time Schedule – Wash-out (Day -2, Day -1)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Smoking abstinence	All day
		Support during smoking abstinence as required	All day
		AE/SAE recording	All day
		Concomitant medication	All day
06:30AM-09:00 AM		Assessment of cough	Day -2 only
Prior to 10:00 AM		Breakfast	
8:00 AM-9:30 AM		CO breath test	
10:00 AM-11:30 AM		Vital Signs	At least 5 minutes in supine position prior to measurement.
12:00 PM-1:30 PM		CO breath test	
Prior to 2:30 PM		Lunch	
4:00 PM-5:30 PM		CO breath test	
Afternoon		Snacks	
In the evening prior to 9:00 PM		Dinner	
8:00 PM-9:30 PM		CO breath test	
		Randomization	Day -1

Abbreviations: AE = adverse event; CO = carbon monoxide; SAE = serious adverse event.

Table 9 Time Schedule – Wash-out (Day 2)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Smoking abstinence	All day
		Support during smoking abstinence as required	All day
		AE/SAE recording	All Day
		Concomitant medication	All day
	√	Plasma nicotine PK sample	24 hours after T_0 of Day 1 (+ 5 minutes)
		Assessment of cough	24 hours (- 30 minutes) after T_0 of Day 1
Prior to 10:00 AM		Breakfast	
8:00 AM-9:30 AM		CO breath test	
10:00 AM-11:30 AM		Vital Signs	At least 5 minutes in supine position prior to measurement.
12:00 PM-1:30 PM		CO breath test	
Prior to 2:30 PM		Lunch	
4:00 PM-5:30 PM		CO breath test	
Afternoon		Snacks	
In the evening prior to 9:00 PM		Dinner	
8:00 PM-9:30 PM		CO breath test	

Abbreviations: AE = adverse event; CO = carbon monoxide; PK = pharmacokinetic; SAE = serious adverse event; T = time point.

9.3.2 Days of Single Use (Day 1 and Day 3)

On the days of single use (Day 1 and Day 3), the following assessments will be performed:

Table 10 Time Schedule – Single Use (Day 1 and Day 3)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Optional: light snacks prior to first blood draw of the day	
		AE/SAE recording	All day

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Concomitant medication	All day
		Support for smoking abstinence as required	All day
		Craving questionnaire (QSU-brief)	First assessment within 15 minutes prior to T_0, 9 assessments thereafter in relation to T_0: 15 min, 30 min, 45 min, 60 min, 2 hr, 4 hrs, 6 hrs, 9 hrs, and 12 hrs after T_0 with a time window of 10 minutes each.
	√	Plasma nicotine sample	A total of 16 blood samples will be taken for a 24-hour profile (Day 1 and Day 3). The first blood sample will be taken within 15 min prior to T_0 and 15 samples thereafter in relation to T_0: T_1 after 2 min + 1 min, T_2 after 4 min + 1 min, T_3 after 6 min + 1 min, T_4 after 8 min + 1 min, T_5 after 10 min + 1 min, T_6 after 15 min + 2 min, T_7 after 30 min + 2 min, T_8 after 45 min + 2 min, T_9 after 60 min + 3 min, T_{10} after 2 hrs + 5 min, T_{11} after 4 hrs + 5 min, T_{12} after 6 hrs + 5 min, T_{13} after 9 hrs + 5 min, T_{14} after 12 hrs + 5 min, and T_{15} after 24 hrs + 5 min (this sample will be drawn during the day following product use, *i.e.,* wash-out).
	√	COHb blood sampling	Five blood samples to be taken, first sample within 15 min prior to T_0, then after 15 min + 2 min, 60 min + 3 min, 4 hrs + 5 min, 12 hrs + 5 min
		CO breath test	First test to be done within 15 min prior to T_0.
		Assessment of cough	Has to be done prior to product use.
6:00 AM-9:00 AM		Start of single product use	
Prior to 10:00 AM		Breakfast	
10:00 AM-11:30 AM		Vital Signs	At least 5 minutes in supine position prior to measurement.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
10:00 AM-11:30 AM		ECG	At least 10 minutes in supine position prior to recording.
12:00 PM-1:30 PM		CO breath test	
Prior to 2:30 PM		Lunch	
4:00 PM-5:30 PM		CO breath test	
Afternoon		Snacks	
Prior to 9:00 PM		Dinner	
8:00 PM-9:30 PM		CO breath test	
8:00 PM-11:00 PM		Product evaluation questionnaire (MCEQ)	
		Collection of used CHTP 1.1 M and mCC butts	After the product use.

Abbreviations: AE = adverse event; mCC = menthol conventional cigarette(s); CHTP 1.1 M= Carbon Heated Tobacco Product 1.1 Menthol; CO = carbon monoxide; COHb = carboxyhemoglobin; ECG = electrocardiogram; MCEQ = modified cigarette evaluation questionnaire; QSU-brief = questionnaire of smoking urges; SAE = serious adverse event; Tx = time point x.

9.4 Discharge

The following assessments will be conducted prior to time discharge on Day 4:

Table 11 Time Schedule – Day 4 Discharge

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Smoking abstinence	Until all laboratory procedures and the spirometry have been performed.
		AE/SAE recording	All day
		Concomitant medication	All day
	√	Plasma nicotine PK sample	24 hrs after T_0 of Day 3 (+ 5 minutes)
		Assessment of cough	24 hours (- 30 minutes) after T_0 of Day 3
	√	Clinical laboratory parameters (hematology, clinical chemistry)	At to be done in at least 10 hours of fasting
		Safety urine analysis	
		Spirometry	Has to be done prior to smoking. At rest for at least 15 minutes prior to spirometry. In sitting position.
Prior to 10:00 AM		Breakfast	
Prior to discharge		Urine pregnancy test	For all female subjects of childbearing potential
Prior to discharge		Vital Signs	At least 5 minutes in supine position prior to measurement.
Prior to discharge		CO breath test	Irrespective of smoking.
Prior to discharge		Physical examination, weight and calculated BMI	
Prior to discharge		Information on the risks of smoking/smoking cessation advice and debriefing	
		Discharge	

Abbreviations: AE = adverse event; BMI = body mass index; CO = carbon monoxide; PK = pharmacokinetic; SAE = serious adverse event; T = time point.

9.5 Safety Follow-up Period

All subjects participating in the product trial on Day -3 will enter a 7-day Safety Follow-up Period.

After discharge at Day 4 (or if prematurely discontinued from the study), subjects will enter a 7-day Safety Follow-up Period.

During the 7-day Safety Follow-up Period, spontaneously reported AEs and SAEs by the subject will be recorded. Any ongoing AEs/SAEs will be actively followed up by the site.

Any AEs or SAEs that are ongoing at the end of the 7-day Safety Follow-up Period will be managed as described in section 8.2.2.

9.6 Early Termination Procedures

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

Table 12 Time Schedule – Early Termination Procedures

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		AE/SAE recording, concomitant medication	All day
	√	Clinical laboratory parameters (hematology, clinical chemistry)	To be done in at least 10 hours of fasting if possible.
		Safety urine analysis	
		Spirometry	To be done 1 hour of not smoking. At rest for at least 15 minutes prior to spirometry. In sitting position.
		Urine pregnancy test	For all female subjects of childbearing potential
		Vital Signs	At least 5 minutes in supine position prior to measurement. For every measurement, it has to be ensured and documented that the duration between the end of last smoking and the measurement should be at least 15 minutes.
		Physical examination, weight and calculated BMI	
		Information on the risks of smoking/smoking cessation advice and debriefing	
		Discharge	

Abbreviations: AE = Adverse Event; BMI = Body Mass Index; SAE = Serious Adverse Event.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

A Clinical Research Associate ("Monitor") from an independent CRO not involved with the study site will be responsible for the monitoring of the study. Monitoring will be performed according to the study CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

The Investigator/head of the investigational site shall permit the Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor so that entries in the CRFs may be verified. The Investigator, as part of their 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 performed and documented.

Subsequent to the Investigator's meeting, and before the first subject is screened, the 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 detailed in the monitoring plan.

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

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

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

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

10.2 Training of Collaborators

An 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 in the relevant systems and other study-specific procedures. The activities of the Investigator's meeting will be described in the monitoring plan.

In addition to the Investigator's meeting, the Investigator 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 to the collaborators involved

in a timely manner. The Investigator will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

GCP regulations require that there are 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 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/head of the investigational site will contact the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.

The Investigator and study 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. In signing this protocol, the Investigator understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All data management activities will be described in detail in the data management plan and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

With the exception of the subject-reported outcome data, all results from the clinical assessments will be recorded in the source documents by the Investigator or their authorized designee(s) and then captured in the CRFs at the study site. The subject questionnaires and the VAS will be entered by the subject directly in the electronic patient-reported outcomes device or in a paper copy. 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 then transferring the data into the CRF, in accordance with the Case Report Form Completion Guidelines.

The Principal Investigator has 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 to attest that the data contained in the CRF are true and accurate. Any corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change and identification of the person making the change. The CRF for each subject will be checked against the source documents at the study site by the Clinical Research Associate. Instances of missing or unclear data will be discussed with the Investigator for resolution. A CRF will be generated for all subjects that sign the informed consent form.

11.1.2 Protocol Deviations

Protocol deviations are defined as those deviations from any procedure as defined in this document, including but not limited to, any violation of inclusion/exclusion criteria, mis-randomizations, use of any nicotine or tobacco-containing product other than the assigned product during each of the exposure period, use of any nicotine tobacco-containing product during wash-out days, assessments not performed or performed outside the scheduled time windows, or use of estrogen or other drugs that are known to affect CYP2A6 activity.

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

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

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

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

11.2 Data Handling

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

All data of all subjects successfully enrolled, as well as subjects who failed Screening, and/or experienced an AE during the study (from time of signing the informed consent form to the end of the safety follow-up period), will be captured and stored in the study database.

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

11.2.1 Data Verification

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

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

11.2.2 Coding

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

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

CHTP 1.1 M issues and/or malfunction: C54451/Medical Device Problem Codes FDA CDRH [23]

11.2.3 Database Lock

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

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

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

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

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

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

12.1.1 Stratification Criteria

For analysis, the following stratification criteria will be used:

- Gender (male and female)
- mCC nicotine level at Admission (ISO nicotine levels ≤ 0.6 mg and 0.6 to 1 mg)

12.1.2 Definitions for Statistical Data Analysis

Unless otherwise stated, for the purposes of statistical analyses, Baseline is defined as the last available time point prior to T_0 on Day 1.

12.1.3 Descriptive Statistics

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

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

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

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

In general, missing data will not be imputed in this study, due to the nature of the measurements and the short periods of exposure and use. However, 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.

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

12.1.5 Significance Level for Inferential Analysis

For all endpoints, unless otherwise stated, statistical tests will be two-sided and conducted at the 5% significance level and all quoted confidence intervals will be two-sided 95% confidence intervals (CI).

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

12.2 Determination of Sample Size and Power Consideration

A total of 48 subjects will be randomized.

The estimates for the within-subject CV for nicotine C_{max} (60%) and $AUC_{(0\text{-last})}$ (50%) are based on the data collected in the ZRHM-PK-05 clinical study [9] comparing the nicotine PK profiles of the Tobacco Heating System 2.2 Menthol, another MRTP candidate, and mCC in a Japanese population.

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

Sample size calculations were conducted using SAS® version 9.2 for the 95% CI of the mean differences between paired observations (proc power onesamplemeans) in the natural log scale [24]. The SAS® implementation of the method published by [25] was adopted to estimate the probability of obtaining at most the target 95% CI of ±30%.

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

12.3 Analysis Populations

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

12.3.1 PK Populations

The PK populations consist of all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations that impact evaluability of the data (to be defined in the SAP) will be included in the PK analysis sets.

12.3.2 Safety Population

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

12.4 Demographics and Baseline Characteristics

Demographic and other Baseline characteristics will be reported for the PK and safety populations. Appropriate summary statistics will be provided as described in section 12.1.3.

12.5 Primary Endpoints

12.5.1 Primary Endpoints Analysis Variables

Nicotine PK parameters will be derived from plasma nicotine versus time data by non-compartmental analysis. In particular:

C_{max}	Maximum observed plasma concentration. C_{max} will be reported as long as there is at least one quantifiable concentration post-exposure
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration (linear trapezoidal method)

12.5.2 Baseline Comparability

Not applicable.

12.5.3 Descriptive Analysis

Primary endpoints will be summarized as described in section 12.1.3.

An analysis of variance (ANOVA) will be conducted on $AUC_{(0\text{-last})}$ and C_{max} endpoints in the natural logarithmic scale. The model will include terms for sequence, subjects within sequence, product exposure, and period as fixed effect factors. The results of this analysis for each of $AUC_{(0\text{-last})}$ and C_{max} are presented in terms of adjusted geometric least square means and 95% confidence intervals for the CHTP 1.1 M:mCC ratio.

This approach is consistent with the guidelines in the European Medicines Agency's guidelines for bioequivalence investigations [26] and FDA's Center for Drug Evaluation and Research [27]. Carry-over effect will not be tested, as it cannot be statistically distinguished from the interaction between treatment and period in a 2x2 crossover [28].

In case of any nicotine levels at T_0 greater than 5% of their C_{max} value being observed, a supportive analysis of the primary endpoints will be performed as described above, where the whereby data of these subjects with nicotine levels at T_0 greater than 5% of their C_{max} value will not be considered for this supportive excluded from the analysis.

A sensitivity analysis will be conducted should there be 20% or more missing PK parameter values by repeating the above analyses using mixed effects ANOVA model including period, sequence, and product exposure as fixed effects and subjects within sequence as a random effect. Additional details will be provided in the SAP.

12.5.4 Confirmatory Analyses

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

12.6 Secondary Endpoints

12.6.1 Secondary Endpoint Analysis Variables

Nicotine PK parameters will be derived as follows:

t_{max}	Time to maximum concentration. t_{max} will be reported as long as there is at least one quantifiable concentration post-exposure
$AUC_{(0\text{-t'})}$	Area under the plasma concentration-time curve from start of product use to the subject-specific time of maximum nicotine concentration following singe use of mCC or CHTP 1.1 M (linear trapezoidal method)
$AUC_{(0\text{-}12)}$	Area under the plasma concentration-time curve from start of product use to the 12 hours time point
$AUC_{(0\text{-}\infty)}$	Area under the concentration-time curve from start of product use extrapolated to time of last quantifiable concentration to infinity, according to: $AUC_{0\text{-}\infty} = AUC_{0-last} + \left(\frac{C_{last}}{\lambda z}\right)$ Where C_{last} is the last quantifiable concentration and λ_z is the terminal elimination rate constant
$t_{1/2}$	Half-life (terminal elimination), derived as $\ln(2)/\lambda_z$, where λ_z is defined as the terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data

More details on PK parameter derivations will be provided in the SAP.

Subjective effects of using CHTP 1.1 M as compared to the mCC will be evaluated by analyzing domain scores of QSU-brief and MCEQ. Full details of questionnaire domain scores derivation will be provided in the SAP.

12.6.2 Baseline Comparability

Not applicable.

12.6.3 Descriptive Analysis

In general, secondary endpoints will be summarized using the approach described in section 12.1.3.

The following analyses will be conducted:

- The $AUC_{(0-\infty)}$, $AUC_{(0-12)}$, $AUC_{(0-t')}$, and $t_{1/2}$ will be analyzed using the same approach adopted for the primary endpoints. Data will be summarized and presented together with 95% CI.
- The Hodges-Lehmann estimates for the median t_{max} differences and 95% CI will be presented [29].
- In case of any nicotine levels at T_0 greater than 5% of their C_{max} value being observed, a supportive analysis of the secondary PK parameters will be performed as described in section 12.5.3, where the data for subjects with nicotine levels at T_0 greater than 5% of their C_{max} value will not be considered for this supportive analysis.
- A mixed effects ANOVA for repeated measurements will be used to analyze the QSU-brief scores over time. Additional details will be provided in the SAP. Summaries will be produced for the QSU-brief scores over time, including the percent change from the value assessed prior to T_0. The maximum percent decrease over time and the time to maximum percent decrease over time will be summarized for the QSU-brief total score by product exposure and analyzed using the Hodges-Lehmann method.
- Levels of exhaled CO and of blood COHb will be summarized over time by means of descriptive statistics reported by product exposure. Analysis of exhaled CO and COHb levels will be conducted using a mixed model for repeated measures, the same approach as for the QSU-brief. COHb levels will be analyzed in the logarithmic scale.
- Mixed effects ANOVA with the same model terms as planned for the sensitivity analysis of the primary endpoints will be adopted for the analysis of the MCEQ domain scores.

12.6.4 Confirmatory Analyses

Not applicable.

12.6.5 Safety Endpoints

In general, all safety data will be listed and tabulated on the safety population by sequence, using the approach described in section 12.1.3.

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, and urine analysis safety panel; concomitant medication and physical examination.

The number and percentage 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 data showing change from Baseline of clinical findings will be provided in listings 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.

12.7 Exploratory Analyses

There are no exploratory analyses currently planned. However, after or during the execution of the planned statistical analyses it may become necessary, useful or of interest to conduct additional analyses in support or to aid the interpretation of the original results; these analyses will be documented and reported as post-hoc analyses.

12.8 Interim Analysis

There are no planned interim analyses.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigator's and Study Administrative Structure

13.1.1 Investigator

Investigator : Fumimasa Nobuoka MD	Ageo Medical Clinic [redacted]

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland Phone: +41 (58) 242 2111 Fax: +41 (58) 242 2811
[redacted], PhD Clinical Scientist	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]
[redacted], MEng MSc Biostatistician	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]
[redacted], MSc Clinical Study Manager	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]
1 May – 31 May 2015 Interim Period	
[redacted], MD Medical Safety Officer	Phone: +41 [redacted] E-mail 1: [redacted] E-mail 2: [redacted]

13.1.3 Other Responsibilities

[redacted] is the local contract research organization designated by PMI to manage and monitor the study: all duties and responsibilities transferred to [redacted] by PMI will be defined in the agreement signed between the two parties.

[redacted]

Responsible person (Clinical Pharmacology): [redacted]

[redacted]

Any SAEs or pregnancies will be handled by:

[redacted]

E-mail: [redacted]

Responsible Medical Safety Officer :

From 1 June 2015 onwards	
[redacted], MD, PhD, MFPM Medical Safety Officer	Phone: +41[redacted] E-mail: [redacted]

Details of the laboratories conducting the clinical safety laboratory services and biopharmaceutical analyses are shown in section 15.2.

13.2 Subject Confidentiality

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

The anonymity of subjects participating in this study will be maintained. 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 date of birth, but **not** by name, initial, or any other details relating to an identifiable person (*e.g.*, address, health insurance identification card, medical chart number, etc.) The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the subject (*e.g.*, the subject's signed study information sheet and 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, health insurance identification card,, 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

The Investigator, head of investigational site and all study site staff involved with the study must permit direct access to source data/documents for study related monitoring, audits, IRB 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, x-rays 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.

X-rays will be evaluated by the investigator who can perform x-ray evaluation. At least the investigator's assessment is required as source documentation. If the actual image is available it can be stored on CD as well.

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 Article 41 of Ministerial Ordinance on GCP [4].

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 E6.

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

- At least 15 years after completion or discontinuation of the study, or
- At least 2 years depending on, for example, the circumstances.
- After formal discontinuation of clinical development of the IP.

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 (if applicable), and enrolment log (if applicable).
- Record of all communications between the Investigator and the IRB, composition of the IRB.
- Record of all communications/contact between the Investigator, Sponsor, and its authorized representatives.
- List of other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, CVs, and their signatures.
- Investigator logs.
- CRFs, study specific questionnaires (and associated data/scoring), subject diaries.
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (*e.g.*, ECGs, x-rays, consultation reports, physical examination, and 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.
- Product issue log, IP accountability logs, dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

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

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

If the head of investigational site wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The head of investigational site must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives.

If the head of investigational site is unable to meet this obligation, he/she 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 as long as the IP is on the market, and/or 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 will be complied with as requested by local requirements.

13.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor. In addition, the Investigators must agree with the Sponsor to commit 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 data, information and trades secretes that are confidential and proprietary to the Sponsor. This document 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, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations.

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 1.1 M 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 trial 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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15 APPENDICES

15.1 Appendix A – Schedule of Events

Table A1 Schedule of Events

	Screening	Admission	Wash-out	Single Use	Wash-out	Single Use	Discharge [k]	Safety Follow-up [l]
Study Day	**-31 to -4**	**-3**	**-2/-1**	**1**	**2**	**3**	**4**	**4 to 11**
Informed consent	•							
Information on the risks of smoking/smoking cessation advice, and debriefing	•	•					•	
Inclusion/exclusion criteria	•	•						
Enrolment		•						
Randomization			• [m]					
Single product use				•		•		
Support during periods of reduced smoking/smoking abstinence (as required)			•	•	•	•		
Product demonstration of CHTP 1.1 M	•							
Product test for CHTP 1.1 M		•						
Identification of current mCC brand	•	•						

	Screening	Admission	Wash-out	Single Use	Wash-out	Single Use	Discharge [k]	Safety Follow-up [l]
Study Day	**-31 to -4**	**-3**	**-2/-1**	**1**	**2**	**3**	**4**	**4 to 11**
Smoking history	●							
Readiness to accept interruption from smoking up to 6 days	●	●						
Willingness to quit smoking in the next 3 months	●							
X-ray [a]	●							
Demographics [b], medical history, concomitant diseases	●							
Prior medication[c]/Concomitant medication	●	●	●	●	●	●	●	●
Physical examination, body height, weight and BMI [d]	●	●					●	
Vital signs [e]	●	●	●	●	●	●	●	
ECG	●			●		●		
Spirometry	●	●					●	
B/U: Hematology, clinical chemistry, urine analysis	●	●					●	
B: Serology	●							
U: Urine drug screen, urine cotinine screen	●	●						
Alcohol breath test	●	●						

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

Abbreviations:

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

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

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

b: Sex, date of birth/age.

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

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

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

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

The first blood sample will be taken within 15 minutes prior to the product use (T_0). Thereafter in relation to T_0, blood will be drawn at the following time points: T_1 after 2 min + 1 min, T_2 after 4 min + 1min, T_3 after 6 min + 1 min, T_4 after 8 min + 1 min, T_5 after 10 min + 1 min, T_6 after 15 min + 2 min, T_7 after 30 min + 2 min, T_8 after 45 min + 2 min, T_9 after 60 min + 3 min, T_{10} after 2 hours + 5 min, T_{11} after 4 hours + 5 min, T_{12} after 6 hours + 5 min, T_{13} after 9 hours + 5 min, T_{14} after 12 hours + 5 min, and T_{15} after 24 hours + 5 min..

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

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

h: A CO breath test will be conducted once on Day -3 and Day 4. On Day -2, Day -1, Day 1, Day 2, Day 3, four breath tests will be done per day. See section 9 for the timing.

i: QSU–brief will be assessed as follows:

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

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

k: All examinations listed in early termination procedures (section 9.6) should also be conducted in subjects prematurely terminating the study.

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

m: Randomization will take place on Day -1.

15.2 Appendix B - Participating Laboratories

Participating laboratories for blood samples testing will be decided prior to the Investigator meeting and site initiation. Safety laboratory samples will be tested at a local laboratory or site.

15.3 Appendix C - Investigational Product and Instructions for Use

The product user guide will be provided as a separate document.

15.4 Appendix D - Abnormal Laboratory Values

Table D1 Abnormal Laboratory Values Rating: Serum Chemistry Parameters

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)
Sodium – Hyponatremia (mmol/L) (1)	<LLN - 130	-	<130 - 120	<120
Sodium – Hypernatremia (mmol/L) (1)	>ULN - 150	>150 - 155	>155 - 160; hospitalization indicated	>160
Potassium – Hyperkalemia (mmol/L)(1)	>ULN - 5.5	>5.5 - 6.0	>6.0 -7.0; hospitalization indicated	>7.0
Potassium – Hypokalemia (mmol/L) (1)	<LLN - 3.0	<LLN - 3.0; symptomatic; intervention indicated	<3.0 - 2.5; hospitalization indicated	<2.5
Glucose – Hypoglycemia (1) (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: (1) 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 (1)	>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 (1) (g/dL) (g/L)	<LLN – 3; <LLN - 30	<3 – 2; <30 - 20	<2; <20	-
Alkaline phosphatase increased (1)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
ALT / AST increased (1)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Gamma-glutamyl transferase (GGT) increased (1)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased (total and direct) (1)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Cholesterol high (1) (mg/dL) (mmol/L)	>ULN - 300; >ULN - 7.75	>300-400; >7.75-10.34	>400-500; >10.34-12.92	>500; >12.92
Triglycerides - Hypertriglyceridemia (1) (mg/dL) (mmol/L)	150 – 300; 1.71 – 3.42	>300 – 500; >3.42 – 5.70	>500 – 1000; >5.70 – 11.40	>1000; >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.

Data Sources:

(1) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

Table D2 Abnormal Laboratory Values Rating: Hematology Parameters

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)
Anemia (Hemoglobin) (1) (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 conseuqences; urgent intervention indicated
Hemoglobin increase (1) – (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 (1) - (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 (1) - (cell/mm^3)	-	>4,000 – 20,000	>20,000	-
Lymphocytes Decrease (1) – (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 (1) - (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 (1) - (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.

Data Source:

(1) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

Table D3 Abnormal Laboratory Values Rating: Urinalysis Parameters

Urine	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)
Protein [(1)]	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	-

Data Source:

(1) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.