



PMI RESEARCH & DEVELOPMENT

Study ZRHM-REXA-07-JP

Clinical Study Report Appendix 16.1.8

Documentation of Statistical Methods

Study Title:	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting
Study Number:	ZRHM-REXA-07-JP
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	01 August 2013
Study Completed (last subject last visit):	03 July 2014
Principal Investigator and Affiliation:	Mamoru Oki, MD, PhD, Seishukai Clinic 3-18-5, Matsugaya, Taitou-ku Tokyo 111-0036, Japan Professor Masahiro Endo, MD, Tokyo Heart Center Osaki Hospital, 5-4-12, Kita-Shinagawa, Shinagawa-ku, Tokyo 141-0001, Japan
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Sponsor Signatories:	Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist Nicola Lama, PhD, Biostatistician Andrea Donelli, Clinical Scientist Patrick Picavet, MD, Medical Safety Officer
Version:	1.0
Date:	24 February 2016

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

This document is confidential. Disclosure of any of its contents to third parties is not permitted except by the prior written consent of Philip Morris Products S.A.



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16.1.8 Documentation of Statistical Methods

16.1.8.1 Statistical Analysis Plan



STATISTICAL ANALYSIS PLAN

A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting

Study Product: Tobacco Heating System 2.2 Menthol

Sponsor Reference No.: ZRHM-REXA-07-JP
CDARO No.: 1001000-8278007

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

Study Sites:
Seishukai Clinic
3-18-5, Matsugaya, Taitou-ku,
Tokyo
111-0036
Japan

Tokyo Heart Center
5-4-12, Kitashinagawa, Shinagawa-ku
Tokyo
141-0001
Japan

Principal Investigators:
W Oki, MD (Seishukai)

M. Endo MD (Tokyo)

**1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES**

By signing this page the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

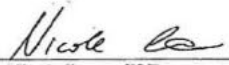
Covance approval:



Andrew Hedge BSc, MSc
Statistician

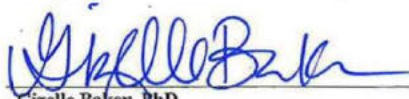
07 NOV 2014
Date

Sponsor approval:




Nicola Lama, PhD
Staff Scientist/ Statistics
Study Biostatistician
Philip Morris Product S.A.

07 NOV 2014
Date




Gizelle Baker, PhD
Manager Epidemiology and Biostatistics
Philip Morris Product S.A.

07 NOV 2014
Date



Christelle Haniza, PhD
Manager Clinical Program THS
Philip Morris Product S.A.

07 Nov 2014
Date



Kausar Aamir, MD, PhD
Medical Safety Officer
Philip Morris Product S.A.

07 Nov 2014
Date



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3 INTRODUCTION

This SAP has been developed to supplement the statistical analysis described in the clinical study protocol (final version 3.0 dated 07 April 2014).

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

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

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

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" ([ICH Guideline E9 1998](#))
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" ([ICH Guideline E3 1995](#))
- Case report forms (eCRF) final version 8.0 (dated 28 July 2014).
- Biostatistical Addendum – Subject Randomization List version 1.0 (08 March 2013).

3.1 Revision History

Version	Date of Revision	Revision
2.0	07 Nov 2014	<ul style="list-style-type: none">• Updated study protocol version in Section 3 and update text in section 6.1 to reflect the new version of the protocol.• Updated Inclusion/Exclusion criteria in Section 6.2 to reflect the text in the protocol.• Updated Blinding in Section 6.3.2 to reflect that the study scientist is unblinded for the data review meeting.• Reworded Section 6.3.3.1 to clarify the product use categorization. Assumption of 50% of exclusive THS 2.2 Menthol for sample size calculation moved to Section 8.• Abstinence category (100% abstinence) biochemically verified with CO breath test in Section 6.3.3.2. Removed the reference to CEMA study because no longer found to be relevant.• Re-organized Section 7.1 in order to concisely describe methods for both urinary BoExp and risk markers. Methods for LLOQ/ULOQ data handling moved in Section 12.1.5.• Specified units for Puff number and frequency, and fixed typo in the Average inter puff interval calculation in Section 7.1.• Included changes from the protocols for Blinding and calculation of %pred values for spirometry in Section 9.• Reworded Analysis population Section 10 in order to clarify the definition of per protocol set which is separately defined on each



Version	Date of Revision	Revision
		<p>analysis period (as defined in Section 11.1.1). Clarified that safety populations may be different pre and post randomization, and that product use categories will be defined over the whole ambulatory period.</p> <ul style="list-style-type: none">• In Section 11.1.1, clarified that:<ul style="list-style-type: none">◦ Product compliance will be defined using the product distribution log in confinement and the eDiary in Ambulatory◦ Non compliance is defined for each period◦ The violation of inclusion criteria 1.2, 4.5 and exclusion criteria 2.18 will be interpreted as impacting evaluability, other violations will be interpreted during the data review• Included in section 11.1.2 procedural violation category and updated concomitant medication category so to include drugs known to affect 11-DTX-B2 and CYP1A2.• Clarified in Section 12.1 that stratified presentation will be performed at period 1 and 4 for the PP set on Baseline characteristics, endpoints for primary objective, and product use.• Summarized in Section 12.1.3 the general methods for descriptive statistics of biomarkers and safety data and removed any related text from each endpoint specific section (Section 12.6.1, 12.6.2, 12.6.2.5, and 12.6.4).• Listed in Section 12.1.3 the TFL labels used for randomized product use and for stratification factors• Clarified the definition of Baseline in Section 12.1.4, using 10:00am on Day 1 as a reference for SA arm• Clarified in Section 12.1.5 the imputation rules for BoExp, CYP1A2, CYP2A6 and risk markers using the last observation carried forward; the missing data handling derivation rules for daily product use for safety and non-safety analysis and summaries. In this section, it was also clarified how the missing dates will be imputed for safety interpretation (for adverse events, diseases, and medications) and for product use calculation• Clarified the definitions of Enrolled subjects and Visit completion status for study subjects in Section 12.2.• Reorganized list of tables, listing and figures following the preparation of the shells, in Sections 12.2 to 13.5• Removed all the tables for the Full Safety population apart from those foreseen in the study protocol (i.e. adverse events and laboratory findings) from Sections 12.2 to 13.5• In Section 12.3.1: the tabulation of mCC brands was limited to brands used by at least 4 subjects; fixed a typo for the definition of the ISO nicotine levels categories. Removed Prochaska questionnaire as not applicable to this study, and readiness to accept interruption and risk of smoking because not included in the data base.• Socio-Economic Status questionnaire data (Section 12.3.2) summarized together with the Baseline characteristics• In Section 12.3.3, clarified that concomitant disease is defined as any condition that was ongoing at Screening. AEs related text



Version	Date of Revision	Revision
		<p>moved into Section 12.6.4.2</p> <ul style="list-style-type: none"> In Section 12.3.4, Debriefing of risk of smoking are removed as not included in the SDTM data base. Product preference and Willingness to use the product will be summarized together with Baseline characteristics. Clarified that the level of CO will serve as compliance tool starting from Day 2, because of possible carry over effect (in Section 12.4) In Section 12.5, text was adapted to the updated definition of analysis periods (1 to 4). Clarified that summaries for the FAS will be produced only if this set differs from the Safety population by more than 10% In Section 12.6.1.1: <ul style="list-style-type: none"> Title was changed so to reflect that the analyzed endpoints were serving for the evaluation of the primary objectives. Clarified the value to be used in the analysis for repeated measurement on analysis day (e.g. COHb at Day 5) A proc GLM approach will be used for the analysis of THS 2.2 and mCC data. Results will be graphed in a Forest plot In Section 12.6.1.3, a sensitivity analysis was added for the analysis of Section 12.6.1.1 by means of a mixed model approach without LOCF missing imputation. Clarified that the sensitivity analysis on the compliant population will be produced also for the comparison between THS 2.2 Menthol and SA. In Section 12.6.2 and 12.6.2.5: <ul style="list-style-type: none"> Added summaries for the endpoints of the primary analysis Clarified that the p-value will only be produced at Day 90 conditionally on the statistical significance at Day 5 Clarified that the CO breath test will be analyzed in the regular scale Text and list of TFL adjusted according to the general rules for summaries of BoExp Summaries of Nicotine and cotinine concentration not produced as a change from baseline and data will be analyzed on the log space. The mixed model code was removed to analyze results using ANCOVA by timepoint for consistency with other analyses. Clarified that the ratio will be estimated for the analysis of nicotine and cotinine C_{peak} and C_{avg} on Day 5. The median difference will be tabulated for the t_{peak} on Day 5. CYP1A2 and CYP2A6 activity will be analyzed in the log space and the THS 2.2 Menthol:mCC ratio will be presented. Percent change from Baseline will be summarized and listed for the QSU-brief. Data will be analyzed



Version	Date of Revision	Revision
		<p>using the same model adopted for the analysis of nicotine and cotinine over study days, amended as appropriate to obtain the required comparison. Only Total score data will be plotted.</p> <ul style="list-style-type: none">Summaries and listing of percent change from Baseline added for mCEQ, MNWS, and Ames mutagenicity. Clarified that for the MNWS the results will be presented for the day prior to the assessment.Section of HST questionnaire data moved within the questionnaires Section 12.6.3.1.Risk markers analyzed for the FAS and PP set. Blood pressure, HbA1c, LDL, HDL, TG, TC, WBC, body weight and waist circumference will be analyzed in the regular scale. 8-epi-PGF2α, 11 DTX-B2, sICAM will be analyzed in the logarithmic scale. Other risk markers will be logarithmically transformed prior to analysis if there is evidence of non-normality by means of Shapiro-Wilks test. <ul style="list-style-type: none">In Section 12.6.4:<ul style="list-style-type: none">Clarified that AE and laboratory findings summaries will be produced also for the Full Safety populationClarified that only product emergent AE will be summarized.Clarified that Pre and post randomization safety data will be summarized separately.Clarified that ambulatory AE data will also be reported by product use category defined on the product use over the whole ambulatory period. No other safety data will be summarized by product use categories, and text was reworded accordingly.Updated that THS 2.2. Device Events will be classified according to a PMI internal device controlled terminology instead of the C54451/Medical Device codes from FDA.Clarified that toxicity grading will be summarized for the laboratory findings together with their changes and shift in normality.Modified any occurrence of "clinical relevance" to "clinical significance".Updated that the spirometry predicted values were standardized according to the predicted set from the Japanese Respiratory Society.Clarified that results from the cough questionnaire will be presented for the day prior to the assessment.
1.0	05JUN2014	<ul style="list-style-type: none">Original version



4 ABBREVIATION OF TERMS AND SPECIAL TERMS

The following abbreviations are used within this SAP.

1-NA	1-aminonaphthalene
1-OHP	Total 1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
8-epi-PGF2 α	8-epi-prostaglandin F2 α
11-DTX-B2	11-dehydro-thromboxane B2
AE/SAE	Adverse Event/ Serious Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic and Chemical
AUC _{0-24 h}	The area under the curve from 0 to 24 h
B[a]P	3-hydroxybenzo(a)pyrene
BMI	Body Mass Index
BoExp	Biomarkers of exposure
CAF	Caffeine
C _{avg}	Weighted average concentration for nicotine or cotinine over 24 hours on Day 5
CC	Conventional Cigarettes
CEMA	2-cyanoethylmercapturic acid
CI	Confidence Interval
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
C _{peak}	The peak nicotine and cotinine plasma concentration
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CV	Coefficient of Variation
CYP1A2	Cytochrome P450 1A2



CYP2A6	Cytochrome P450 2A6
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of Study
FAS	Full analysis set
FEV ₁	Forced Expiratory Volume in 1 second
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced Vital Capacity
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HEMA	2-hydroxyethyl mercapturic acid
HIV	Human Immunodeficiency Virus
HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
hs-CRP	High sensitive C-reactive protein
HST	Human Smoking Topography
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
ITT	Intention-to-treat
(b)	Interactive Web Response System
LDL	Low density lipoprotein
LLOQ	Lower Limit of Quantification
LS	Least Squares
mCC	Single preferred brand of menthol CC
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenyl mercapturic acid
MNWS	Minnesota Nicotine Withdrawal Scale
MR	Mean ratio
NEQ	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol



NNN	Total N-nitrososonornicotine
NRT	Nicotine replacement therapy
NSAIDS	nonsteroidal anti-inflammatory drugs
o-tol	o-toluidine
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred Term
PX	Paraxanthine
QC	Quality Control
QSU-brief	Questionnaire of Smoking Urges Brief
QTcB	QT Interval Corrected using Bazett's Formula
QTcF	QT Interval Corrected using Fridericia's Formula
SA	Smoking abstinence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
sICAM-1	Soluble inter-cellular adhesion molecule-1
SOC	System Organ Class
SOP	Standard Operating Procedure
S-BMA	S-benzylmercapturic acid
S-PMA	S-phenylmercapturic acid
TC	Total cholesterol
TFL	Tables, Figures, and Listings
TG	Triglycerides
THS	Tobacco Heating System
t _{peak}	Time to peak concentration
ULOQ	Upper Limit of Quantification
UV	Ultra violet
VAS	Visual Analogue Scale
WBC	White blood cells



WHO World Health Organisation
YG1024+S9 Ames Mutagenicity test



The following special terms are used in this SAP:

Baseline period	06:30 AM at Day -1 until 06:29 AM of Day 1.
Menthol conventional cigarette (mCC)	The term 'menthol conventional cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
mCC incompatible with Human Smoking Topography (HST) device	All mCCs that are incompatible with the HST device (e.g., slim mCC).
Day of Discharge from confinement	Day 6: when the subject is released from the site (confinement period) prior to entering into the ambulatory period.
Day of discharge from ambulatory period	Day 91: when the subject is released from the site on Day 91 and enters the 28-day safety follow-up period.
Enrollment	On Day -2 eligible subjects are enrolled after all inclusion and exclusion criteria have been satisfactorily met and the subject is willing and ready to use THS 2.2 Menthol (the test of THS 2.2 Menthol is the last assessments prior to enrollment).
Exposure period	06:30 AM of Day 1 until time of discharge on Day 91
Randomization	Assignment of the subject randomization number in the Interactive Web and Voice Response System (b) (4). This can be done any time on Day 0, however, subjects are not to be informed of their randomization group prior to Day 1.
Run-in period	Time of admission to the site until 06:29 AM of Day -1
Safety follow-up	After the time of Discharge on the Day 90 Visit, a 28-day safety follow-up will be done for the recording in eCRF of spontaneously reported new adverse events / serious adverse events (AEs/SAEs) and the active follow-up of ongoing AEs/SAEs by the study site.
Screen failure	Subjects who are not enrolled will be considered a screen failure and will be replaced by other subjects.
Tobacco Heating System 2.2 Menthol (with Menthol Tobacco Sticks) (THS 2.2 Menthol)	THS 2.2 Menthol comprises the following components: Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable.



5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objectives and Endpoints

1. To demonstrate the reduction of primary biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) (except Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL)) in a confinement setting in smokers switching from menthol conventional cigarettes (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints:

- Monohydroxybutenyl mercapturic acid (MHBMA) 24-hour urine concentration adjusted for creatinine on Day 5.
 - 3-hydroxypropylmercapturic acid (3-HPMA) 24-hour urine concentration adjusted for creatinine on Day 5.
 - S-phenylmercapturic acid (S-PMA) 24-hour urine concentration adjusted for creatinine on Day 5.
 - Carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.
2. To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoint:

- Total NNAL 24-hour urine concentration adjusted for creatinine on Day 90 Visit.

5.2 Secondary Objectives and Endpoints

1. To evaluate self-reported nicotine/tobacco product use including dual-use in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).

Endpoint:

- Number of mCC or Menthol Tobacco Sticks used daily as reported on the log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.

2. To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints:

- Quantity Excreted in urine over 24 hours for MHBMA, S-PMA and 3-HPMA.
- Carbon monoxide (CO) (expressed as ppm) in exhaled breath.



- Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine on Day 5 and on Day 90 Visit:
 - Total 1-hydroxypyrene (1-OHP),
 - Total N-nitrosornicotine (NNN),
 - 4-aminobiphenyl (4-ABP),
 - 1-aminonaphthalene (1-NA),
 - 2-aminonaphthalene (2-NA),
 - O-toluidine (o-tol),
 - 2-cyanoethylmercapturic acid (CEMA),
 - 2-hydroxyethyl mercapturic acid (HEMA),
 - 3-hydroxybenzo(a)pyrene (B[a]P),
 - 3-hydroxy-1-methylpropyl-mercapturic acid (HMPMA),
 - S-benzylmercapturic acid (S-BMA).
3. To describe the levels of primary and secondary BoExp over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.
- Endpoints (on Days 1 to 5, Day 30 Visit, Day 60 Visit and Day 90 Visit):
- CO (expressed as ppm) in exhaled breath.
 - COHb in blood (expressed as % saturation of Hemoglobin).
 - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine:

• MHBMA.	• 2-NA.
• 3-HPMA.	• o-tol.
• S-PMA.	• CEMA.
• Total NNAL.	• HEMA.
• 1-OHP.	• B[a]P.
• Total NNN.	• HMPMA.
• 4-ABP.	• S-BMA.
• 1-NA.	
4. To determine the levels of nicotine over the entire exposure period (confinement and ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.
- Endpoints:
- Nicotine equivalents (NEQ) (expressed in quantity excreted and concentration adjusted for creatinine) in 24-hour urine from Day 1 to Day 5, Day 30 Visit, Day 60 Visit and Day 90 Visit.
 - Nicotine and cotinine in plasma from Day 1 to Day 4, Day 5, and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.



5. To describe the pharmacokinetic (PK) profiles of nicotine and cotinine in smokers in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints:

- Peak (highest concentration value along the day) on Day 5.
- Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
- Weighted average concentration over 24 hours on Day 5.

6. To describe the change in Cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.

Endpoint:

- Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5 and Day 90 Visit.

7. To monitor the safety profiles during the study.

Endpoints:

- AEs, SAEs and device events, including THS 2.2 Menthol malfunction and misuse.
- Respiratory symptoms: cough assessment by visual analogue scale (VAS), Likert scales, and one open question.
- Vital signs.
- Spirometry.
- Electrocardiogram (ECG).
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medications.

8. To monitor selected risk markers in a confinement and ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoints:

- Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
- Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.



- White blood cell (WBC count), including count of differentials, and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-prostaglandin F_{2α} (8-epi-PGF_{2α}) and 11-dehydro-thromboxane B₂ (11-DTX-B₂) in 24 hour urine on Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as quantity excreted and concentration adjusted for creatinine).
- Body weight and waist circumference on Day 90 Visit.

5.3 Exploratory Objectives and Endpoints

1. To describe the following parameters in a confinement and/or ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:

Endpoints:

- Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24 hour urine.
- Subjective effect of smoking: Questionnaire of Smoking Urges (QSU-brief questionnaire); questionnaire Minnesota Nicotine Withdrawal Scale (MNWS)-Revised on Day 5 and Day 90 Visit, and nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire score on Day 90 Visit.
- Cytochrome P450 2A6 (CYP2A6) activity: in plasma on Day 6, and on Day 90 Visit using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.

2. To evaluate in smokers switching from mCC to THS 2.2 Menthol, and smokers continuing smoking mCC the relationship between NEQ and¹:

Endpoints:

- NEQ in urine by:
 - Blood COHb.
 - MHBMA in urine.
 - 3-HPMA in urine.
 - S-PMA in urine.
 - Exhaled CO.
 - 1-OHP in urine.
 - Total NNN in urine.
 - 4-ABP in urine.
 - 1-NA in urine.
 - 2-NA in urine.
 - o-toI in urine.
 - CEMA in urine.
 - HEMA in urine.
 - B[a]P in urine.
 - HMPMA in urine.
 - S-BMA in urine.
 - Total NNAL in urine.
- Selected risk markers:
 - NEQ in urine by
 - hs-CRP in serum
 - homocysteine in serum
 - blood glucose in serum
 - LDL in serum

¹ The reporting of this objective will be subject of a separate report.



- | | |
|------------------------|---------------------------------|
| - HDL in serum | - sICAM-1 in serum |
| - TG in serum | - WBC count in blood |
| - TC in serum | - Platelet count in blood |
| - Fibrinogen in plasma | - 8-epi-PGF2 α in urine. |
| - HbA1c in blood | - 11-DTX-B2 in urine. |

All biomarkers measured in urine will be expressed as quantity excreted and concentration adjusted for creatinine.

3. To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing smoking mCC:

Endpoints:

- The subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ).
- HST questionnaire
- The following parameters measured per cigarette from the HST device.

- Total number of puffs.	- Total smoking duration.
- Total puff volume.	- Total work.
- Average puff volume.	- Average work.
- Average puff duration.	- Average pressure drop.
- Total puff duration.	- Average peak pressure drop.
- Average flow.	- Smoking intensity.
- Peak flow.	- Puffing time index.
- Total inter puff interval.	- Puff frequency.
- Average inter puff interval.	

4. To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol:

Endpoint:

- Combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
- Filter analysis: smoke nicotine in filter and ultra-violet (UV) absorbance at 310 nm (during confinement setting only).

5. To describe the product use over the course of the study according to the product preference of the subject.

Endpoint:

- Number of mCC or Menthol Tobacco Sticks smoked daily as reported on the usage log during the confinement period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary by product preference.



5.4 Additional Endpoints

The following additional assessments will be made:

- Serology for Hepatitis B and C.
- Urine pregnancy test (females only), urine cotinine test, urine drug screen
- Alcohol breath test.
- Socio-Economic Questionnaire.
- Question on product preference.
- Chest X-ray.

5.5 Study Hypotheses And Evaluation Criteria

5.5.1 Hypotheses

The hypothesis to be tested is that the geometric mean level of the BoExp for THS 2.2 Menthol is lower relative to mCC.

For the primary analyses, the hypothesis will be tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and on Day 90 Visit for Total NNAL according to the primary and secondary objectives. For the secondary analyses, the hypothesis will be tested on Day 5, and if significant on Day 90 Visit.

5.5.2 Evaluation Criteria

The study will be considered successful if the study demonstrates a 50% reduction or more in MHBMA, 3-HPMA, S-PMA, and COHb on Day 5, and in Total NNAL at the Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, using a one-sided test with 2.5% type I error probability.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a randomized, controlled, open-label, 3-arm, parallel group, multi-center study. Randomization is stratified by sex and average daily mCC consumption over the last 4 weeks as reported during the Screening Visit (10 - 19 mCC/day vs. >19 mCC/day). (Figure 1).

In total, 160 eligible, healthy smoking subjects were planned to be randomized into one of the three study arms in Table 1.

**Table 1 Definition of Study Arms**

Study arm	Number of subjects
THS 2.2 Menthol	80
mCC	40
Smoking abstinence	40

However, one of the sites was closed down after a good clinical practice failure, and 160 subjects were randomized at the Tokyo Heart Centre site along with those subjects randomized at the Seisukai site prior to the site being shut down.

This is an *ad libitum* smoking study. In general, smoking/product use during the confinement period will be allowed between 06:30 AM and 11:00 PM. During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from 08:00 AM to around 23:00 PM on Day 30, Day 60, and Day 90. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted. During the second day of the Day 30 and Day 60 Visits, product use will be allowed from 06:30 AM onwards. On the second day of the Day 90 Visit, product use will be allowed after the CYP2A6 activity, MNWS and cough questionnaires and spirometry have been performed until time of discharge.

The Screening Visit will be conducted within 4 weeks prior to Admission to the investigational site (Day -30 to Day -3). Screening procedures do not necessarily have to be conducted on the same day. During the Screening Visit the study collaborator will demonstrate the use of THS 2.2 Menthol.

Prior to enrollment on Day -2, as the last procedure of the eligibility assessments, subjects will have a product test of the THS 2.2 Menthol (use of up to 3 THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product test will only be done after pregnancy is excluded by a negative urine pregnancy test. Enrollment takes place after all inclusion and exclusion criteria have been satisfactorily met. Only subjects willing and able to use the product will be enrolled in the study.

Subjects are admitted and enrolled on Day -2, but not randomized until Day 0. From Day -2 to Day 0, all subjects continue smoking their single preferred brand of mCC and baseline values will be recorded. On Day 0, subjects will be randomized to one of the 3 study arms (Table 1). Subjects will be informed of their product allocation by the study site staff on Day 1 prior to 06:30 AM.

The exposure period (from Day 1 06:30 AM until time of Discharge on Day 91) will include both the exposure in confinement and the exposure in the ambulatory setting.

The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product between 06:30 AM and 11:00 PM in THS 2.2 Menthol and mCC arms. Subjects allocated to the SA arm will be asked to abstain from smoking. Subjects have been



allowed to smoke their normal cigarettes prior to Day 1. Subjects will be provided with psychological support during the period of smoking abstinence. No medication to support SA will be allowed during the confinement period. Use of any tobacco/nicotine-containing product other than the assigned product/regimen will not be allowed and may, at the discretion of the Investigator, result in the withdrawal of the subject from the study.

On Day 6, the safety procedures will be conducted before discharge of the subject from the clinic. Use of products will be allowed on Day 6 in the THS 2.2 Menthol and mCC arms, but only after the CYP2A6 activity, MNWS and cough questionnaires and spirometry have been performed.

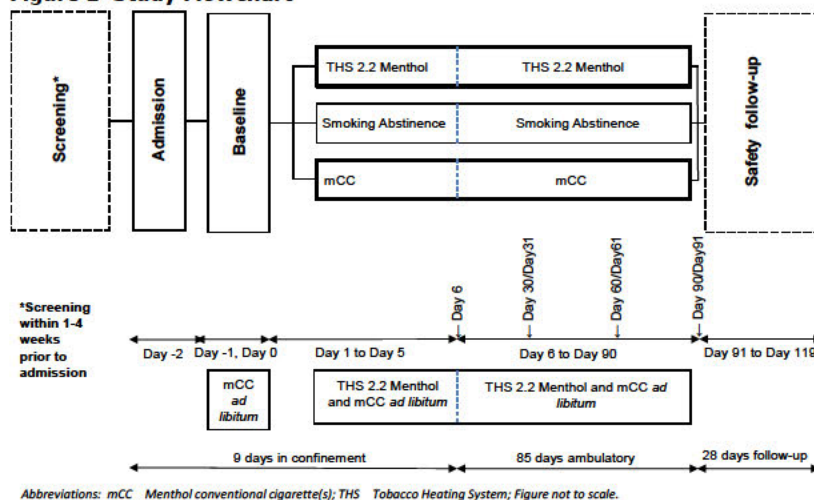
At the end of the confinement period (Discharge from the site on Day 6), subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 85 days. Subjects will be allowed to use nicotine replacement therapy (NRT) if considered necessary by the Investigator or requested by the subject.

Subjects will be required to make three site visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) during the ambulatory period. Each visit will cover 2 consecutive days on site. For all Visits the subject will check-in in the morning prior to 08:00 AM on the first day and will check-out on the second day.

The use of THS 2.2 Menthol will be strictly forbidden for subjects in the mCC or SA arms.

During the ambulatory period, subjects will not be withdrawn from the study for the use of nicotine/tobacco-containing products other than the assigned product/regimen. Subjects will record in a product use electronic diary any use of mCC (menthol or non-menthol), NRT, or other nicotine/tobacco-containing products on a daily basis.

After the time of Discharge on the second day of the Day 90 Visit, subjects will enter a 28-day safety follow-up period during which there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found. The end of the study (EOS) is defined as the time of Discharge plus 28-day follow-up.

**Figure 1 Study Flowchart**

6.1.1 Timing of Confinement Period

The 9 day confinement period consists of:

- The Admission Day (Day -2).
- The run-in period is from admission on Day -2 until 06:29 AM of Day -1.
- The baseline period is from Day -1, 06:30 AM until Day 1, 06:29 AM.
- The exposure period in the confinement setting is from Day 1 06:30 AM until Day the time of Discharge on Day 6 (start of the ambulatory setting).

The exposure period in the ambulatory setting is from the time of discharge on Day 6 to the time of Discharge on the second day of the Day 90 Visit.

6.2 Selection of Study Population

6.2.1 Inclusion Criteria

The following inclusion criteria will be applicable for this study:

1. Subject has signed the informed consent form (ICF) and is able to understand the information provided in the Subject Information Sheet and ICF.
2. Subject is aged from 23 to 65 years (inclusive).
3. Subject is Japanese.



4. Smoking, healthy subject as judged by the Investigator based on all available assessments from the Screening period/Day of Admission (e.g. safety laboratory, spirometry [FEV₁/FVC >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV₁ >80% predicted value, and post-bronchodilator FVC >80% predicted value], vital signs, physical examination, ECG, chest X-ray and medical history).
5. Subject smokes at least 10 commercially available mCCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/mCC 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).
6. The subject does not plan to quit smoking in the next 3 months.
7. The subject is ready to accept interruptions of smoking for up to 90 days.
8. The subject is ready to accept using the THS 2.2 Menthol.

6.2.2 Exclusion Criteria

The exclusion criteria are:

1. As per Investigator judgment, the subject cannot participate in the study for any reason (e.g. medical, psychiatric and/or social reason).
2. A subject who is legally incompetent, physically or mentally incapable of giving consent (e.g. emergency situation, under guardianship, prisoners or subjects who are involuntarily incarcerated).
3. The subject has medical condition requiring smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary and cardiovascular disease or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Investigator.
4. The subject has a body mass index (BMI) <18.5 or ≥32 kg/m².
5. As per Investigator 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.
6. The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
7. The subject has received medication (prescription or over the counter) within 14 days or within 5 half-lives of the drug (whichever is longer) prior to the Admission Day (Day -2) which has an impact on CYP1A2 or CYP2A6 activity.
8. If a subject has received any medication (prescribed or over the counter) within 14 days prior to Screening or prior to the Admission Day (Day -2), it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives and subject's safety.



9. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid.
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 the study.
11. The subject has a positive urine drug test.
12. Positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B or hepatitis C.
13. Donation or receipt of whole blood or blood products within 3 months prior to Admission.
14. The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling or child).
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 or child).
16. The subject has participated in a clinical study within 3 months prior to the Screening Visit.
17. The subject has previously participated in the same study at a different time (i.e. each subject can be included in the study population only once).
18. For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission), or is breast feeding.
19. For women only: Subject does not agree to use an acceptable method of contraception*.

* Intrauterine device, intrauterine system, established use of oral/injectable/implantable/transdermal hormonal methods, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the safety follow-up period

6.3 Product Allocation and Blinding

6.3.1 Methods of Assigning Subjects to Product Arms

Randomization will be conducted through the (b) (4)
(b) (4) (b) (4)

Subjects will be randomized to one of the 3 arms. Each sex and each of the current mCC consumption levels (10 to 19 mCC/day and >19 mCC/day) will have a quota applied to ensure they represent at least 40% of the total study population.

Four separate randomization lists were provided (male smokers who smoke 10-19 mCC/day, female smokers who smoke 10-19 mCC/day, male smokers who smoke >19 mCC/day, and female smokers who smoke >19 mCC/day). Block randomization was used within each stratum (i.e., each list) in a 2:1:1 ratio (THS 2.2 Menthol:mCC:SA).

The randomization scheme will be generated by a statistical division within (b) (4) and none of the study team (Sponsor and Covance), investigators and study subjects will be exposed to the live randomization codes prior to randomization.



6.3.2 Blinding

This is an open-label study; therefore, the subjects and investigators will be unblinded to subject's product assignment after randomization. However, there will be a limited degree of blinding during the conduct of the study including the data review and data analysis process. In particular, PMI and Covance personnel will be blinded to the randomized product as summarized in the following table (Table 2: Blinding Scheme):

Table 2: Blinding Scheme

Blinded Study Personnel	End of Blinding Period
PMI and Covance study statisticians	After the SAP finalization or database lock ¹ , whichever comes last.
PMI study data managers	After the finalization of PMI blind database review ¹ .
PMI safety and clinical scientist	After the finalization of PMI blind database review ¹ . Can be actively un-blinded before that time point in case of the occurrence of any safety question, when appropriate.

¹ As part of the PMI Quality Control (QC) activity, data listings will be reviewed by Covance and PMI before database lock, with no access to the randomization information. Full details will be available in the data review plan.

The study scientist will be unblinded for the data review meeting, therefore the role of blinded reviewer is delegated. Any PMI and Covance personnel who are not listed in the above table will be unblinded by default.

No data will be made available from the unblinded study team to blinded study team without a dummy randomization or masking in place, and any communications among the two groups will avoid the use of subject randomization information until database lock. PMI will receive blinded data for the pre-analysis data review as planned in the data review plan.

6.3.3 Compliance to Product Allocation

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 Menthol and mCC in THS 2.2 Menthol and mCC arms, respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each Tobacco Stick/mCC when requested by the subject. During the ambulatory period, the subjects randomized to the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects randomized to the SA arm will be instructed to abstain from smoking.

In addition, in subjects in the SA arm, the compliance will be chemically verified in confinement using exhaled CO breath. The cut-off point for the CO breath test value to distinguish CC use vs. no CC use will be 10 ppm (Benowitz et al. 2002). No subjects



from the SA arm will be withdrawn from the study if their exhaled CO breath test results are >10 ppm.

6.3.3.1 Dual-use

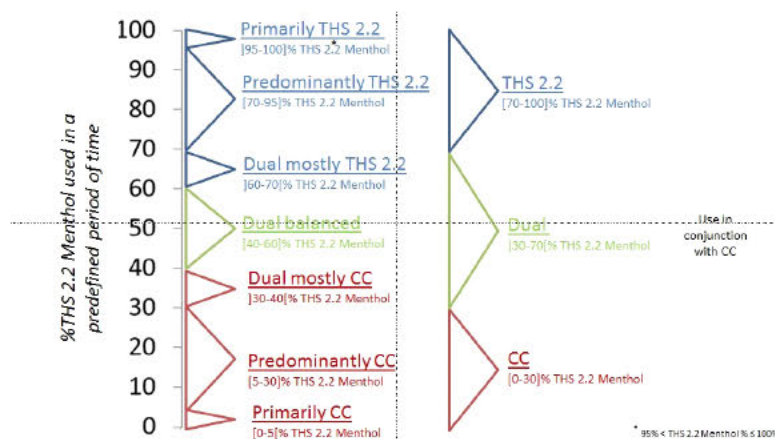
Although subjects are being requested to use solely the product/regimen allocated to them in their respective study arm, it is considered that during the ambulatory period not all subjects randomized to the THS 2.2 Menthol and SA arms might be exclusively using THS 2.2 Menthol or being abstinent at all times during the study. Subjects may concomitantly use THS 2.2 Menthol and CC (dual-use) or smoke some CC in the SA arm.

To assess dual-use of THS 2.2 Menthol and CC, PMI has defined product use categories defined by the percentage of the reported THS 2.2 Menthol Tobacco Sticks consumption during each time period of interest. The percentage use of THS 2.2 Menthol will be calculated by:

$$100 \times \frac{\text{Total number of THS 2.2 Menthol products used}}{\text{Total number of THS 2.2 Menthol products used} + \text{Total number of CC smoked (menthol and/or non-menthol)}}$$

Product use categories are summarized in Table 20, and Figure 2 presents a detailed overview of their definition.

Figure 2 – Product Use Pattern Categorization





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

6.3.3.2 Abstinence from mCC use

In order to further optimize the assessment of BoExp and increase the comparability of the levels of BoExp between THS 2.2 Menthol and SA the confounding effects of the use of any other tobacco or nicotine containing product (other than the assigned product) needs to be controlled for. Therefore a subject will be considered abstinent based on the following categorization:

- “Abstinence”: full abstinence from tobacco or nicotine containing product use other than the assigned product, biochemically verified with CO breath test ≤ 10 ppm.
- “Predominantly abstinence”: not more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average and no more than two uses on a single day.
- “Not abstinent”: more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average or more than two uses on a single day.

7 DERIVED AND COMPUTED VARIABLES

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

Mean percent change from baseline is the mean of all individual subjects’ percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual subject’s baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject’s baseline value and multiplying by 100. These individual subjects’ percent changes from baseline values will be used to calculate the mean percent change from baseline.

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

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

$$QTcB = \frac{QT}{\sqrt[3]{\frac{60}{HR}}}$$



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

$$QTcF = \frac{QT}{\sqrt[3]{60/HR}}$$

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

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

7.1 Biomarkers

7.1.1 Biomarkers of Exposure and Risk Markers in Urine

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

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

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

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

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

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

7.1.2 Nicotine Equivalents

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

$$\begin{aligned} \text{NEQ [mg]} &= (\text{free nicotine}_c [\mu\text{mol/l}] + \text{nicotine-glucuronide}_c [\mu\text{mol/L}] \\ &+ \text{free cotinine}_c [\mu\text{mol/l}] + \text{cotinine-glucuronide}_c [\mu\text{mol/L}] \\ &+ \text{free trans-3'-hydroxycotinine}_c [\mu\text{mol/L}] \\ &+ \text{trans-3'-hydroxycotinine-glucuronide}_c [\mu\text{mol/L}]) \\ &* 162.2 [\mu\text{g}/\mu\text{mol}] * \text{urine volume (l)} / 1000 [\mu\text{g}/\text{mg}] \end{aligned}$$

N.B. All concentrations must be in $\mu\text{mol/L}$ before applying the above formula.



The conversion factors will be applied as follows:

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

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

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

where the concentrations are measured from the same 24 hour urine collection.

7.1.3 CYP1A2

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

The conversion factor will be applied as follows:

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

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

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

7.1.4 CYP2A6

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

The conversion factor will be applied as follows:

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

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

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

7.2 Pharmacokinetic Parameters

The peak nicotine and cotinine plasma concentration (C_{peak}) and time to peak concentration (t_{peak}) will be obtained directly from the concentrations taken on Day 5. If the peak concentration occurs at more than one time point then t_{peak} will be assigned to the first value. The weighted average concentration over 24 hours on Day 5 (C_{avg}) will be calculated by dividing the area under the curve from 0 to 24 h (AUC_{0-24h}) by 24, where the AUC_{0-24h} is calculated using the linear trapezoidal rule.

Since the samples are taken whilst the subjects are smoking freely all samples must be non-missing for the parameters to be calculated as C_{peak} (and t_{peak}) could occur at any time.



7.3 Questionnaires

7.3.1 Socio-Economic Status Questionnaire

On Day 4, subjects will fill a socio-economic status (SES) questionnaire. Subjects will be asked a series of questions related to their education, occupation, size and monthly income of their household.

7.3.2 Fagerström Test for Nicotine Dependence (FTND)

The FTND will be used in its revised version (Heatherton et al 1991), as updated in 2012 (Fagerström et al. 2012). These questions are to be answered by the subject themselves. It is conducted at Screening to determine subject's dependence on nicotine and on the Day 90 Visit to assess any changes in their dependence on nicotine.

Table 3 describes the six questions the questionnaire consists of, and the scores associated with each question.

The FTND total score will be derived by summing the individual item scores if all items are non-missing, otherwise the total score will be set to missing. For the FTND total score, descriptive statistics and frequency tables according to the following classification will be provided (Fagerström et al. 2012):

Mild	0 – 3
Moderate	4 – 6
Severe	7 – 10

**Table 3: Scoring for the Fagerstrom Test for Nicotine Dependence**

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

7.3.3 Questionnaire of Smoking Urges-Brief (QSU-brief)

The QSU-brief (Cox et al. 2001) is a self-reported questionnaire completed on a daily basis from Day -1 to Day 5, and on every visit during the ambulatory period, i.e., Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90).

The QSU-brief consists of 10 items as presented in Table 4.

**Table 4: Questionnaire of Smoking Urges Brief - Questions and Factors**

	Question	Factor
1	I have a desire for a cigarette right now	1
2	Nothing would be better than smoking a cigarette right now	2
3	If it were possible, I probably would smoke now	1
4	I could control things better right now if I could smoke	2
5	All I want right now is a cigarette	2
6	I have an urge for a cigarette	1
7	A cigarette would taste good now	1
8	I would do almost anything for a cigarette now	2
9	Smoking would make me less depressed	2
10	I am going to smoke as soon as possible	1

All items will be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge to smoke.

Two factor scores and a total score will also be derived (Cox et al. 2001). Each factor is a subset that includes 5 of the 10 questions as defined in Table 4. Factor 1 represents the desire and intention to smoke with smoking perceived as rewarding, while Factor 2 represents an anticipation of relief from negative effect with an urgent desire to smoke.

The factors and total scores will be calculated by averaging non-missing item scores if at least 50% are non-missing, otherwise the factor or total score will be set to missing.

7.3.4 Modified Cigarette Evaluation Questionnaire

The MCEQ (Cappelleri et al. 2007) will be completed by the subject him/herself on a daily basis from Day -1 to Day 5 and on every ambulatory visits on Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90). On Day -1 and Day 0, all subjects will complete the questionnaire. From Day 1 onwards, only subjects who are randomized to the THS 2.2 Menthol and mCC arms will complete this questionnaire.

The MCEQ consists of 12 items as presented in Table 5.

**Table 5: Modified Cigarette Evaluation Questionnaire - Questions and Subscales**

	Question	Subscale
1	Was smoking satisfying?	Smoking Satisfaction
2	Did cigarettes taste good?	Smoking Satisfaction
3	Did you enjoy the sensation in your throat and chest?	Enjoyment of Respiratory Tract Sensations
4	Did smoking calm you down?	Psychological Reward
5	Did smoking make you feel more awake?	Psychological Reward
6	Did smoking make you feel less irritable?	Psychological Reward
7	Did smoking help you concentrate?	Psychological Reward
8	Did smoking reduce your hunger for food?	Psychological Reward
9	Did smoking make you dizzy?	Aversion
10	Did smoking make you nauseous?	Aversion
11	Did smoking immediately relieve your craving for a cigarette?	Craving Reduction
12	Did you enjoy smoking?	Smoking Satisfaction

Items are assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity on that scale.

The subscales scores will be derived by averaging the individual non-missing item scores if at least 50% are non-missing, otherwise the subscale score will be set to missing.

7.3.5 Minnesota Nicotine Withdrawal Scale (revised edition) Questionnaire

The MNWS (Hughes and Hatsukami 2008) is a 24 hour recall that will be completed by the subject him/herself daily from Day 0 to Day 6, and on the second day of every visit during the ambulatory period. From Day 0 to Day 6 only, MNWS questionnaire must be asked prior to start of product use/smoking and no later than 10:00 AM. On Day 31 and Day 61 the assessment of MNWS will be conducted irrespective of the time of product use but no later than 10:00 AM. Whilst on Day 91 the assessment of MNWS has to be conducted prior to smoking but no later than 10:00 AM.

The self-reported part of the MNWS consists of the following 15 items which are rated over the last 24 hours on a scale of 0 to 4 (see Table 6). Higher scores indicate greater intensity on that scale.

The total score will be derived by calculating the average of all the non-missing data from the first 9 items. If more than 50% of the first 9 items are missing then the total score will be set to missing.

**Table 6: Minnesota Nicotine Withdrawal Scale (Revised Edition)
Questionnaire Scores**

	Question	Total Score
1	Angry, irritable, frustrated.	Yes
2	Anxious, nervous.	Yes
3	Depressed mood, sad.	Yes
4	Desire or craving to smoke.	Yes
5	Difficulty concentrating.	Yes
6	Increased appetite, hungry, weight gain.	Yes
7	Insomnia, sleep problems, awakening at night.	Yes
8	Restless.	Yes
9	Impatient.	Yes
10	Constipation	No
11	Dizziness	No
12	Coughing	No
13	Dreaming or nightmares	No
14	Nausea	No
15	Sore throat	No

7.3.6 Human Smoking Topography Questionnaire

Subjects will be asked by the Investigator to complete the HST questionnaire on:

- Day 0 for all subjects smoking mCC compatible with the HST SODIM[®] device (i.e., non-slim mCC)
- Day 4, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90) for all subjects in the THS 2.2 Menthol and mCC arms (except mCC which are not compatible with the HST SODIM[®] device).

The HST questionnaire has 5 items rated on a 5-point scale (from strongly agree to strongly disagree). The items are:

1. The smoking of the conventional cigarettes/products is different with the device.
2. You enjoy smoking with the device as much as without it.
3. The taste of the conventional cigarettes/products is different with the device.
4. The device is easy to use.
5. Your smoking is disturbed by the device.

7.3.7 Cough Assessment

Subjects will be asked to assess the respiratory symptom 'cough' on a VAS, on three Likert scales, and with one open ended question on a daily basis during the confinement period (from Day 0 to Day 6), and on the second day of each ambulatory period visit (Day 30 Visit, Day 60 Visit and Day 90 Visit). From Day 0 to Day 6, assessment of cough is done prior to start of product use/smoking and no later than 10:00 AM. On Day 31, Day 61 assessment of cough will be conducted irrespective of the start of product



use and not later than 10:00 AM. On Day 91 the assessment of cough will be conducted prior to smoking/product use but no later than 10:00 AM.

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

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

Subjects will also be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales as presented in [Table 7](#).

Table 7 : Cough Assessment Likert Scales

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

7.4 Human Smoking Topography Assessment

The HST SODIM[®] device measures and records the flow and other per-puff parameters listed below ([Table 8](#)) on Days 0, 1, 4 and the first day of each ambulatory visit. From the per-puff parameters, the per-cigarette parameters shown below will be derived (representing average values or totals per cigarette) ([Table 9](#)).

Prior to calculation of the per-cigarette parameters, the topography data will be processed through analysis software. Only data that are declared "accepted" by the software will contribute to the per-cigarette parameters and will be part of the study database.

**Table 8: HST- Per-Puff Parameters**

Description	Variable	Unit
Puff number	N_i	puff
Puff volume	V_i	mL
Puff duration	D_i	s
Average flow [V_i/D_i]	Q_{mi}	mL/s
Peak flow	Q_{ci}	mL/s
Inter puff interval	I_i	s
Sum of I_i and D_i	DF_i	s
Work [$\int P_{mi} \cdot FinalFlow \cdot dt$]	W_i	mJ
Average pressure drop	P_{mi}	mmWG
Peak pressure drop	P_{ci}	mmWG
Average resistance [P_{mi}/Q_{mi}]	R_{mi}	mmWG/mL/s
Peak resistance [P_{ci}/Q_{ci}]	R_{ci}	mmWG/mL/s

**Table 9: HST - Per-Cigarette Parameters**

Description	Variable	Formula	Unit
Total number of puffs	NPC	$\sum N_i$	puff
Total puff volume	TVOL	$\sum V_i$	mL
Average puff volume	AvgVi	$\sum V_i / NPC, i=1 \dots NPC$	mL
Average puff duration	AvgDi	$\sum D_i / NPC, i=1 \dots NPC$	s
Total puff duration	TDi	$\sum D_i$	s
Average flow	AvgQmi	$\sum Q_{mi} / NPC, i=1 \dots NPC$	mL/s
Peak flow	AvgQci	$\sum Q_{ci} / NPC, i=1 \dots NPC$	mL/s
Total inter puff interval	Tli	$\sum I_i$	s
Average inter puff interval	Avgli	$\sum I_i / NPC, i=1 \dots NPC$	s
Total smoking duration	TDFi	$\sum DF_i$	s
Total Work	TWi	$\sum W_i$	mJ
Average Work	AvgWi	$\sum W_i / NPC, i=1 \dots NPC$	mJ
Average pressure drop	AvgPmi	$\sum P_{mi} / NPC, i=1 \dots NPC$	mmWg
Average Peak pressure drop	AvgPci	$\sum P_{ci} / NPC, i=1 \dots NPC$	mmWg
Smoking Intensity	SMINT	$TVOL/TDF_i$	mL/s
Puffing Time Index	PTI	$(100 \cdot TD_i)/TDF_i$	%
Puff Frequency	PFeq	$NPC/(TDF_i/60)$	puff/min

7.5 Categorical Variables

The categorical variables used in this study are shown [Table 10](#) below. Additional categorical variables used for stratification are reported in [Table 20](#).

Table 10: Categorical Variables Definitions

Variable	Categories
BMI (kg/m ²)	Underweight: <18.5 Normal range: ≥ 18.5 and < 25.0 Overweight: ≥ 25.0 and < 30.0 Obese: ≥ 30.0
FTND total score	Mild: 0 - 3 Moderate: 4 - 6 Severe: 7 - 10

**Table 10: Categorical Variables Definitions**

Variable	Categories
CO breath test level (ppm)	≤ 10 > 10
COHb level	≤ 2% > 2%
Adverse event severity	Mild Moderate Severe
Adverse event relationship	Related Not related
Adverse event expectedness	No Yes
Action taken with study product due to adverse event	Product use interrupted Product use stopped Product use reduced Not applicable None
Outcome of adverse event	Death related to adverse event Not recovered or not resolved Recovered or resolved Recovered or resolved with sequelae Recovering or resolving Unknown
Seriousness Criteria	Fatal Life-threatening Requires hospitalization Results in disability/incapacity Congenital anomaly/birth defect
Severity of device event	Major Minor

8 SAMPLE SIZE JUSTIFICATION

The following discussion addresses the ability to demonstrate on Day 5 a reduction of at least 50% on four selected primary BoExps and on Day 90 on a fifth primary BoExp in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.



Table 11 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 Menthol and the two control arms in COHb, 3-HPMA, MHBMA and S-PMA on Day 5 based on data from a controlled, randomized, open-label, 3-arm parallel single-center confinement study to investigate exposure to selected smoke constituents in smokers switching from CCs to smoking article (SMAR) cigarettes for 5 days, the YVD-CS01-EU study (ClinicalTrials.gov: ID: NCT00812279) sponsored by PMI. The mean ratios and CVs for SMAR/CC are expected to be the same as THS 2.2 Menthol/mCC.

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

	THS 2.2 /CC MR (CV)	THS 2.2 /SA MR (CV)
COHb	0.40 (0.32)	2.10 (0.20)
3-HPMA	0.30 (0.50)	1.70 (0.33)
MHBMA	0.15 (0.70)	1.00 (0.35)
S-PMA	0.20 (0.70)	1.15 (0.42)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = conventional cigarettes; COHb = carboxyhemoglobin; CV = coefficients of variation; MHBMA = monohydroxybutenyl mercapturic acid; MR = mean ratios; S-PMA = S-phenylmercapturic acid; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Table 12 describes the expected CV and MR between THS 2.2 Menthol and the mCC control arm in Total NNAL on Day 90 based on data from a Philip Morris USA-sponsored randomized, controlled, switching, open-label, parallel-group, single-center study in 90 male and female adult smokers evaluated six biomarkers of tobacco smoke exposure over a 12-week period (Frost-Pineda et al., 2008). The mean ratios and coefficients of variations for EHCJLI /CC are expected to be the same as THS 2.2 Menthol/mCC.

Table 12: Expected Mean Ratios and Coefficients of Variation for THS 2.2 Menthol/mCC

	THS 2.2 Menthol/mCC MR (CV)
Total NNAL	0.30 (0.60)

Abbreviations: Total NNAL = total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; MR = mean ratios; THS 2.2 = Tobacco Heating System 2.2.

Table 13 describes the expected CV and MR between THS 2.2 Menthol and the mCC control arm in COHb, 3-HPMA, MHBMA, S-PMA based on data from a single-center, open-label, randomized, controlled, 2-arm parallel group study to evaluate the exposure to selected smoke constituents in smoking, healthy subjects switching from CC to THS 2.1 compared to subjects continuing to smoke CC for 5 days, the ZRHX-EX-01 study (ClinicalTrials.gov: ID: NCT01780714) sponsored by PMI. The mean ratios and coefficients of variations for THS 2.1/CC are expected to be the same as THS 2.2 Menthol/mCC.

**Table 13: Coefficients of Variation (ZRHX-EX-01 study)**

	THS 2.2 Menthol/mCC MR (CV)
COHb	0.44 (0.14)
3-HPMA	0.28 (0.20)
MHBMA	0.11 (0.47)
S-PMA	0.07 (0.50)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = conventional cigarettes; COHb = carboxyhemoglobin; CV = coefficients of variation; MHBMA = monohydroxybutenyl mercapturic acid; MR = mean ratios; S-PMA = S-phenylmercapturic acid; THS 2.2 = Tobacco Heating System 2.2.

Based on these two sets of assumptions on the mean ratios and coefficients of variations for the four primary BoExp on Day 5, the power to demonstrate a reduction was computed. Subjects are expected not to have any reason for exclusion from the PP Set in the confinement period for THS 2.2 Menthol arm and in ambulatory and confinement condition for the mCC arm.

Fifty percent of the subjects are expected to be excluded from the PP Set in the THS 2.2 Menthol arm in the ambulatory (mostly due to lack of compliance to the randomized product). Thus the expected populations on which the reductions will be assessed as described in [Table 14](#).

Table 14: Sample Size to Assess the Reductions

	Sample size to assess the reduction (THS 2.2 Menthol:mCC)
COHb	80:40
3-HPMA	80:40
MHBMA	80:40
S-PMA	80:40
Total NNAL	40:40

[Table 15](#) describes the expected power to demonstrate a reduction on all 5 primary BoExps in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and ZRHX-EX-01 given a sample size of 160 smokers (~80 in THS 2.2 Menthol, ~40 in mCC, and ~40 in the SA arm).

**Table 15: Expected Power (YVD-CS01-EU and ZRHX-EX-01 Studies Assumptions)**

Assumptions	Reduction					
	50%	51%	52%	53%	54%	55%
YVD-CS01-EU	94%	88%	81%	70%	56%	38%
ZRHX-EX-01	98%	97%	92%	76%	41%	6%

A total of 160 smokers (80 in THS 2.2 Menthol, 40 in mCC, and 40 in the SA arms) were to be randomized over both sites. However due to the the site that terminated due to ICH/GCP non-compliance 219 smokers were randomized, so that the 160 smokers would be recruited at the Tokyo Heart Center, to demonstrate a reduction of at least 50% on all 5 primary BoExp in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability. The calculation of the sample size was based on the assumption that 50% of the subjects in the THS 2.2 Menthol arm would be using THS 2.2 Menthol exclusively at Day 90.

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

The term “adjusted to creatinine” has been replaced by “adjusted for creatinine” in all relevant endpoints and analyses.

The second exploratory objective (“To evaluate in smokers switching from mCC to THS 2.2 Menthol, and smokers continuing smoking mCC the relationship between NEQ and:

- Primary and secondary BoExp
- Selected risk markers and NEQ)

will be reported in a separate report.

Serology for human immunodeficiency virus (HIV) 1/2 cannot be transferred because of privacy laws, therefore this endpoint will not be presented in listings.

The PMI and Covance study statisticians will be unblinded after finalization of the SAP or database lock, whichever is later.

The PMI study scientist will be unblinded for the data review meeting, therefore the role of blinded reviewer is delegated.

Listing and summaries of spirometry predicted values will be presented standardized to the predicted set from the Japanese Respiratory Society, as measured by the spirometry devices.



10 ANALYSIS POPULATIONS

In pivotal pharmaceutical / therapy studies the general approach is to analyze the intention-to-treat (ITT) population. In such studies the product efficacy and the product compliance are generally highly correlated as the product effects may be detectable by the subject (e.g., relief from symptoms). Therefore, the ITT population is used to account for the effects of the product compliance. The drivers for product use (ultimately product compliance) for tobacco products are not the same as in a pharmaceutical setting. Smokers decide to smoke, despite the known risks and adverse health effects, based on social, cultural, personal, and psychological factors. Therefore the ITT approach may not be optimal in randomized studies evaluating modified risk tobacco products, as these products are targeting risk reduction which may not be the main factor influencing the choice of tobacco products used by the subjects.

The aim of this study is to demonstrate the optimal effect that could be achieved by the use of THS 2.2 in terms of reduction in BoExp. The following considerations were taken into account in order to measure “optimal effect” in this study:

1. The primary analysis is designed to assess the effect in subjects who are compliant with the assigned product use, rather than the effect in the full population. The full population would represent a heterogeneous exposure (e.g., as mixed product use, or non-use of the assigned product) rather than a THS 2.2 Menthol exposure.
2. The subjects are allowed to use the THS 2.2 Menthol product in a truly *ad libitum* setting (smoking is not restricted based on the number of CC smoked prior to study onset).

The optimal effect may be a somewhat ideal scenario, which differs from the real-world effect (effect under actual use setting) mainly by reducing the impact of non-compliance on the estimate. To be able to assess real-world effects we are planning to conduct studies, both in our clinical program (6 months exposure response studies) and in our perception and behavior program (actual use studies). In order to fully understand the full range of the potential effect THS 2.2 once it is commercialized it will be important to understand both the optimal effect and the real-world effect.

The PP Set will be the primary analysis for BoExp, and risk markers. The full analysis set will be the primary analysis set for compliance to randomization arm. Exposure and questionnaires will be described by randomization arm and according to product use categories (see [Table 20](#)).

A sensitivity analysis will be run on the compliant population for the for BoExp and risk markers.

Safety will be analyzed using the safety population and the full safety population by randomization arm and according to the product use categories (see [Table 20](#)).



10.1 Full Analysis Set

The FAS consists of all the randomized subjects who had at least one post-randomization product use experience, if randomized to THS 2.2 Menthol or mCC, and have at least one valid non-safety assessment (THS 2.2 Menthol, mCC, and SA arms). Subjects that were enrolled at the site that terminated due to ICH/GCP non-compliance will be excluded from the FAS.

10.2 Per Protocol Set

The PP set is a subset of the FAS and includes all randomized subjects who have no major protocol deviations impacting evaluability as defined in [Table 16](#) (see [section 11.1.1 "Major Protocol Deviations"](#)).

The PP set is assessed for each product use time period 1 to 4 (see [Table 20](#)), considering the product deviations occurring only that period, independent of any exclusion from the population in previous periods.

10.3 Safety Populations

10.3.1 Safety Population

Before randomization, the safety population consists of all the subjects who had at least one exposure to THS 2.2 Menthol (including the product test at Admission Day). This also includes any randomized subjects who had no valid safety assessment post-randomization.

After the randomization, the safety population includes all randomized subjects who had at least one valid safety assessment post-randomization. Subjects in the safety populations will be analyzed according to product use categories defined over the whole ambulatory period.

Although subjects that were enrolled at the site that was terminated due to ICH/GCP non-compliance will be excluded from the safety population, they will be summarized within the Full Safety Population (see [section 10.3.2 "Full Safety Population"](#)).

10.3.2 Full Safety Population

The full safety population consists of all the subjects who had at least one exposure to THS 2.2 Menthol (including the product test at Admission Day). Safety evaluation will be presented before and after randomization as for the Safety population (see [section 10.3.1 "Safety Population"](#)).

10.4 Compliant Population

The compliant population will be a subset of the PP Set for subjects from the THS 2.2 Menthol arm who are exclusive THS 2.2 Menthol users, as defined in [Section 10 "Analysis Populations"](#), or for subjects from the mCC arm who are exclusive users of



mCC, or for subjects in the SA arm who are abstinent, as defined in [Section 6.3.3.2](#) "Abstinence from mCC use".

11 PROTOCOL DEVIATIONS

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

Information following site monitoring and other reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and subsequently recorded in an electronic data capture (EDC) system. Additional protocol deviations may be identified in the data review, these will also be recorded in the EDC system.

Additional protocol deviations (e.g. time windows for assessments) may be identified through programmatic checks and entered in ADaM datasets.

All deviations will be reviewed to determine their severity/impact when subjects are assigned to analysis populations. Each deviation will be classified as major or minor; all major deviations will be further reviewed to determine whether or not the deviation impacts the evaluability of the results and therefore should result in the subject being excluded from the PP Set.

11.1.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (per period of the study) to determine whether they will be excluded from any of the analysis populations. This will take place during the pre-analysis data review meeting prior to database lock. The categories for the major deviations will include, but are not limited to the deviations presented in [Table 16](#).

**Table 16: Definition of Major Protocol Deviations**

Category	Description
Mis-randomization	Being administered the wrong product according to the randomization schedule.
Product compliance	<u>Confinement:</u> Use of any nicotine or tobacco-containing product other than the assigned product, using the product distribution log. Exhaled CO breath test >10 ppm for subjects from the SA arm starting from Day 2. <u>Ambulatory:</u> Non compliance in the THS 2.2 Menthol and SA arms will be defined for each period. Non compliance is based on product use reported in the product use Diary for Periods 2 - 4, as any of the following occurrence: - Use of more than 2 CC in a single day during the period. - Average product use from Day 1 through the end of the period is more than 0.5 CC per day.
Violation	Violation of inclusion/exclusion criteria.
Duration of 24 hour collection	Start and end times not within the 30 min window.

Among the violation of inclusion/exclusion criteria, only violations of inclusion criteria 1, 2, 4, 5 or of the exclusion criteria 2, 18 will be interpreted as impacting evaluability and lead to exclusion from the PP Set. Any violations of other inclusion or exclusion criteria will be assessed for their impact on the PP Set and evaluated during the pre-analysis data review meeting.

11.1.2 Minor Protocol Deviations

The categories for the minor deviations will include, but are not limited to the deviations presented in [Table 17](#).

Table 17: Definition of Minor Protocol Deviation Categories

Category	Description
Concomitant medication	Use of drugs which are known to affect 11-DTX-B2, CYP2A6 or CYP1A2 activity.
Procedural violation	Violation of planned procedure
Time deviation (Questionnaires)	Assessments not taken at the correct time or within the allowed time window (see Table 18)

**Table 17: Definition of Minor Protocol Deviation Categories**

Category	Description
Time deviation (Blood draws)	Assessments not taken at the correct time or within the allowed time window (see Table 18)
Time deviation (CYP1A2 activity)	Assessments not taken at the correct time or within the allowed time window (see Table 18)
Time deviation (CYP2A6 activity)	Assessments not taken at the correct time or within the allowed time window (see Table 18)
Time deviation (Assessment of cough)	Assessments not taken at the correct time or within the allowed time window (see Table 18)
Time deviation (CO breath test)	Assessments not taken at the correct time or within the allowed time window (see Table 18)
Time deviation (HST Recording)	Assessments not taken at the correct time or within the allowed time window (see Table 18)
Visit window deviation	Day 30, Day 60 and Day 90 Visits outside of visit window (see Table 18).
Time missing	Assessment date or time is missing
Assessment missing	Assessment is missing
Visit missing	Scheduled visit not done

11.1.3 Assessment Windows

During the confinement period, smoking of the randomized products should take place within the 06:30 AM and 11:00 PM window.

The assessment windows are shown in [Table 18](#).

Table 18: Assessment Windows

Assessment	Nominal Time point(s)	Window
24 h urine sample	Start (Days -1 to 5)	06:30 AM \pm 20 min
	Start (Days 30, 60 and 90)	09:00 AM \pm 20 min
	End (Days 0 to 6)	06:29 AM \pm 20 min
	End (Days 31, 61 and 91)	08:59 AM \pm 20 min
CYP1A2 activity in plasma	Day 0, Day 5 and Day 90	6 h \pm 15 min after intake of caffeine tablet



Assessment	Nominal Time point(s)	Window
CYP2A6 activity	Day 0, Day 6 and Day 91	Prior to smoking / product use
CO breath test	Day -2	Time of admission to 06:30 PM irrespective of product use
	Morning (Days -1 to 5)	To be done within 15 minutes prior to smoking/product use (for THS 2.2 Menthol and mCC arms) or between 08:00 AM and 09:30 AM (SA arm)
	Day -1 to Day 5	Between 12:00 PM and 01:30 PM, 04:00 PM and 05:30 PM, and 08:00 PM and 09:30 PM
	Day 6	Prior to discharge
	Day 30 and Day 60	Between 10:00 AM and 11:30 AM. Irrespective of product use
Assessment of Cough	Day 90	Between 10:00 AM and 12:30 AM. Irrespective of product use
	Days 0 to 6	To be done prior to product use but not later than 10:00 AM.
	Day 31 and Day 61	Irrespective of product use but no later than 10:00 AM
MNWS questionnaire	Day 91	Prior to smoking but no later than 10:00 AM
	Day 0 to 6	To be done prior to product use but not later than 10:00 AM
	Day 31 and Day 61	Irrespective of product use but no later than 10:00 AM
QSU-brief questionnaire	Day 91	To be done prior to product use but not later than 10:00 AM
	Days -1 to 5, Days 30, 60 and 90	08:00 PM to 11:00 PM
mCEQ questionnaire	Days -1 to 5, Days 30, 60 and 90	08:00 PM to 11:00 PM
	Days 0 to 4	08:00 PM to 09:30 PM



Assessment	Nominal Time point(s)	Window
Nicotine and cotinine in plasma	Day 5 for THS 2.2 Menthol and mCC arms: within 15 minutes before first product use (T0); then additional blood samples at 2 hour intervals from T0 until 11:00 PM. In SA arm only one blood sample between 08:00 PM to 09:30 PM	Each sample has a 5 minute time window
	Day 6 for THS 2.2 Menthol and mCC arms: 20 and 24 h after T0 of Day 5. In SA arm only one blood sample between 08:00 AM to 09:30 AM.	5 minute time window
COHb blood sampling	Days -1 to 4 Morning sample on Day 5	08:00 PM to 09:30 PM Within 15 minutes prior to product use (for THS 2.2 Menthol and mCC arms) or between 08:00 AM and 09:30 AM (SA arm)
	Day 5 other samples	Between 12:00 PM and 01:30 PM, 04:00 PM and 05:30 PM, and 08:00 PM and 09:30 PM
	Day 30 and Day 60	Irrespective of product use between 10:00 AM and 11:30 AM.
	Day 90	Irrespective of product use between 10:00 AM and 12:30 AM.
HST Questionnaire	Day 0	08:00 PM-11:00 PM
	Day 4, Day 30, Day 60 and Day 90 for all subjects in the THS 2.2 Menthol and mCC arms	08:00 PM-09:30 PM
HST Recording	Day 0	06:30 AM-11:00 PM
	Day 1 and Day 4 for all subjects in the THS 2.2 Menthol and mCC arms smoking compatible mCC	06:30 AM-11:00 PM
	Day 30, Day 60 and Day 90 for all subjects in the THS 2.2 Menthol and mCC arms smoking compatible mCC	Start time: 08:30 AM to 09:30 AM. End time: 12:30 PM to 01:30 PM. 4-hour recordings \pm 15 min
Ambulatory Visit	Day 30 Visit, Day 60 Visit and Day 90 Visit	\pm 3 days.



12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Data analysis will be performed using SAS[®] Version 9.3.

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

12.1.1 Stratified Presentation

The following summaries will be produced by randomization arm, stratified by sex (male vs. female) and mCC consumption (10-19 mCC/day vs. >19 mCC/day) for the PP set at period 1 and 4:

- Demographics and Baseline Characteristics
- COHb, and MHBMA, 3-HPMA, S-PMA and total NNAL adjusted for creatinine.
- Product use

Summaries of data by product use categories will be produced for the product use time periods 1 to 4 (see [Table 20](#)), as appropriate.

Summaries of safety data will be provided stratified by pre-randomization and randomized period (see [Table 20](#)).

All endpoints will be summarized stratified by time point as appropriate.

12.1.2 Subgroup Analyses

No subgroup analyses will be performed in this study.

12.1.3 Descriptive Statistics

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), 95% confidence interval (95% CI), median, first and third quartiles, minimum and maximum; for log-normal data the geometric mean, geometric 95% confidence interval and geometric coefficient of variation (CV) will also be presented instead of the SD and 95% CI of the arithmetic mean. For categorical data, frequency counts and percentages will be presented. Data listings will include all subject level data collected unless otherwise specified.

Unless otherwise specified, data described over time will be reported for the 2 – 4 periods (see [Table 20](#)).



Data for early termination will be summarized at the end of the corresponding period (1-4). Data for early termination collected during an unplanned ambulatory visit will be handled as specified in Section 12.1.6 "Handling of Unplanned Data".

Urinary BoExp Summaries

In general, urinary BoExp will be described over time as follows:

- Summary of concentration values adjusted for creatinine, and their percent change from baseline. Line graphs will be produced for arithmetic means of creatinine adjusted concentration (and 95% CI of the mean) for the percent change from baseline over all timepoints.
- Summary of quantity excreted over 24-hours values.

In general, BoExp measured in blood or breath tests will be described with summaries of the levels over time and levels expressed as percent change from baseline. BoExp levels will also be presented with line graphs.

Summaries and graphs will be produced for the FAS and PP Set. All derived variables will be listed together with the raw BoExp levels.

Safety Summaries

In general, summaries for the Safety and Full Safety populations will be produced by randomization arm, separately for the following periods:

- Pre-Randomization, including safety data collected until randomization. Only for this period, the Safety population includes any subjects who tested the product but were not randomized and these subjects will be reported in a separate "Product Test Only" group.
- Randomized period, including Baseline and all post-Baseline data.

The following product labels will be used throughout the TFLs (Table 19):

Table 19: Product Labels

Product	Format used in TFLs	Order in TFLs
Tobacco Heating System 2.2 Menthol	THSm2.2	1
Menthol conventional cigarettes	mCC	2
Smoking abstinence	SA	3

The following stratification labels (Table 20) for the TFLs will be used:

Table 20: Stratification Labels

Stratification Factor	Label (Definition)
Product preference (which product the subject would prefer to be randomized to).	THSm2.2 (THS 2.2 Menthol) mCC SA NP (No preference)



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Sex	Male Female
Daily mCC consumption	10-19 >19
Safety Time Periods	Pre-Randomization period ([Product trial – Randomization]) Randomized period Confinement ([Day 1-Day 6 confinement]) Ambulatory ([Day 6 ambulatory-Day 90 Visit]) Safety Follow-up ([Day 90 Visit – End of Study])
Product Use Time Periods	Period 1 ([Day 1-Day 6 confinement]) Period 2 ([Day 6 ambulatory-Day 30 Visit]) Period 3 ([Day 30 Visit-Day 60 Visit]) Period 4 ([Day 60 Visit-Day 90 Visit])
Product Use Categories for mCC arm	CC Only (Exclusively CC) CC Dual (Use of other products)
Product Use Categories for SA arm	Abstinent Predominantly Abstinent Not Abstinent
General Product Use Categories for THS 2.2 Menthol arm	THS 2.2 [70-100%] Dual [30-70%] CC [0-30%]
Detailed Product Use Categories for THS 2.2 Menthol	Primarily THS 2.2 ([95-100]%) Predominantly THS 2.2 ([70-95]%) Dual Mostly THS 2.2 ([60-70]%) Dual Balanced ([40-60]%) Dual Mostly CC ([30-40]%) Predominantly CC ([5-30]%) Primarily CC ([0-5]%)

Unless otherwise defined, the text in brackets () will be used to define the labels in the TFL footnotes

12.1.4 Definitions for Statistical Data Analysis

The following definitions (Table 21) for statistical analyses/presentations will be used:

Table 21: Definition of Terms for the Statistical Analysis

Term	Definition
Baseline Value	The last subject's assessment prior to subject's first randomized product use in mCC / THS 2.2 Menthol arms. In the SA arm, the subject's last assessment prior to 10:00



AM on Day 1

Where the baseline is different for any of the variables measured this will be specified in the relevant section.

In this SAP, references to the Day 30 Visit, Day 60 Visit and Day 90 Visit, Day 30, Day 60, and Day 90 refer to the nominal days.

Nominal Day 31 will be referred to as the second day of the Day 30 Visit. Nominal Day 61 will be referred to as the second day of the Day 60 Visit. Nominal Day 91 will be referred to as the second day of the Day 90 Visit.

For urine collections taken on Days x to y, e.g., Days 5 to 6, these will be referred to as collected on Day x, e.g., Day 5, in the SAP.

12.1.5 Handling of Dropouts or Missing Data (including outside the limits of quantification)

For laboratory parameters:

Values below the lower limit of quantification (LLOQ) will be imputed using LLOQ/2. For values above the upper limit of quantification (ULOQ), the ULOQ will be imputed.

The number of values below LLOQ or above ULOQ will be presented in each summary table. If 50% or more data are below LLOQ or above ULOQ, only the number (%) of value below LLOQ or above ULOQ will be reported in the summaries, together with minimum and maximum of the observed values.

Missing data at Baseline will not be imputed.

For BoExp:

- A last observation carried forward (LOCF) approach will be implemented to replace all missing data with the last available data for each parameter being assessed.
- For parameters assessed at several timepoints during a visit, the last available data at the timepoint being assessed collected at previous study visit will be used in the analyses. For example, if on Day 5, the evening assessment (20:00-23:00) is missing for COHb, the evening assessment from Day 4 will be used for analysis regardless whether other COHb assessments are available at Day 5.

For daily product use data in safety summaries:

- Product use categories will be defined based on percentage of THS 2.2 Menthol use calculated by averaging non missing consumption data over the entire ambulatory time interval.

For daily product use data in non-safety analyses and summaries:

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

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

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

For missing or partial dates:

- Missing dates for Day 30, 60, and Day 90 Visits will be imputed for the calculation of product use exposure within periods by adding 30, 60, or 90 days to the randomization date. If the imputed date falls after discharge date (e.g. for early terminated subjects), then the discharge date will be used.
- Missing or Partial dates will not be imputed for Adverse Events (AEs), for medical history, and for concomitant medications, but assumptions will be made as follows to assign them to specific analysis categories:



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

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

12.1.5.1 Insufficient Data for Analysis/Presentation

If there are no values or events at the general value then the break out should not be presented. For example if the number of AEs related to study procedure is zero then the presentation by severity of related events will not be produced.

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

For categories of continuous data summaries that have <4 subjects no summaries will be shown.

12.1.6 Handling of Unplanned Data

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

12.1.7 Multiple Comparisons / Multiplicity

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

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

12.2 Disposition of Subjects

A subject is considered:

- Enrolled if he/she was randomized or if not randomized he/she performed the product trial and he/she confirmed to be willing to use the product.



- Completed Confinement, Completed Day 30, Day 60, Day 90 Visits if he/she did not discontinue until the discharge at Day 6, Day 31, Day 61, and Day 91 respectively.

The number and percent of subjects will be summarized for the following categories: subjects screened, screening failures that tried product, screening failures that did not try product, enrolled subjects, enrolled and not randomized, randomized subjects, completed confinement, completed Day 30 Visit, completed Day 60 Visit, completed Day 90 Visit, completed study, and discontinued (if applicable discontinued subject that never used their allocated products will be identified).

Inclusion and exclusion criteria will be listed as to whether the subjects have met or not met the criteria.

All subjects who fail to complete the study will be categorized by their primary reason for discontinuation and summarized by randomization arm for the FAS. Disposition of subjects and reasons for discontinuation will also be summarized separately. Supportive listings will be provided.

The number and percent of randomized subjects with protocol deviations will be summarized by randomization arm for the PP Set and Safety Population broken down by main deviation category (major/minor), sub-categories and evaluability. Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

The number and percent of randomized subjects included in each analysis population will be summarized by randomization arm for the Full Safety Population. For subjects excluded from the analysis populations this will be broken down by reason for exclusion. Subjects will be counted once per exclusion, and can be counted for more than one exclusion.

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.1	Summary of Subject Disposition – All Screened Subjects
15.2.1.2	Summary of Reasons for Discontinuations – FAS
15.2.1.3.1.1	Summary of Protocol Deviations – PP Set
15.2.1.3.1.2	Summary of Protocol Deviations – Safety Population
15.2.1.3.2	Analysis Sets and Reasons for Exclusion from Analyses – Full Safety Population



TFL number	Title
LISTINGS	
15.3.1.1	Listing of Inclusion/Exclusion Criteria
15.3.1.9	Listing of Subject Disposition, Randomization and Assignment to Analysis Sets
15.3.1.11	Listing of Protocol Deviations
15.3.2.3	Listing of Subjects and Observations Excluded from Analysis Populations
16.1.7	Listing of Randomization Schemes and Codes

12.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized for the Safety Population, FAS and for the PP set in periods 1 - 4.

The demographic variables age, sex, race, body weight, height, BMI and waist circumference will be summarized by randomization arm, and by the two stratification factors (sex, and mCC consumption). Other baseline characteristics will also be included in the table.

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – PP Set
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – PP Set
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set
LISTINGS	
15.3.1.8	Listing of Demographics

12.3.1 Current Cigarette Brand and Smoking Characteristics

The following smoking characteristics at Admission (Day -2) will be summarized and listed as specified in [Section 12.3 “Demographics and Other Baseline Characteristics”](#): ISO tar yields (continuous and categorized as 1-5 mg, 6-8 mg, 9-10 mg and >10 mg), ISO nicotine level (continuous and categorized as ≤0.6 mg and > 0.6 mg), and number of mCCs smoked (categorized as 10-19 cig/day and >19 cig/day). The summaries will be presented for the Safety Population, FAS and PP Set.



Current mCC brand(s) smoked by the subject and recorded at Screening will be summarized for the FAS. Only brands used by at least 4 subjects will be tabulated. An "other" category will contain all the brands used by less than 4 subjects. All the data at Screening and Admission (Day -2) will be listed by randomization arm and study day.

Smoking history, including whether subjects have smoked for at least the last three consecutive years and the subject's mCCs consumption any during the previous 4 weeks will be listed by randomization arm at Screening and Admission (Day -2) where applicable

Data will be listed and summarized as presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – PP Set
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – PP Set
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set
15.2.1.5	Summary of Current Cigarette Brands At Screening – FAS
LISTINGS	
15.3.1.2	Listing of Current Cigarette Brands
15.3.1.3	Listing of Smoking History

12.3.2 Socio-Economic Status Questionnaire

Subject answers will be listed. The number and percentage of subjects in each category from each question apart from questions 5a and 5b will be summarized, and presented in listings as shown below. For question 5a the number and percent of subjects in categories 1-11, 12 and 13 will be presented and then the number and percent of subjects in each of the categories 1-11. For question 5b the number and percent of subjects who answered categories 12 or 13 from question 5a will be presented for categories 1-2, 3 and 4. In addition the number and percent of subjects in categories 1 and 2 will be presented. The summaries will be presented for the Safety Population, FAS and PP Set.



TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – PP Set
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – PP Set
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set
LISTINGS	
15.3.1.12	Listing of Socio-Economic Questionnaire Results

12.3.3 Medical History and Concomitant Diseases

Medical history is defined as any condition that started and ended prior to Screening. Concomitant disease is defined as any condition that was ongoing at Screening.

Medical history and concomitant disease will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 or later and listed separately by randomization arm, System Organ Class (SOC) and Preferred Term (PT) within SOC.

Medical History and concomitant disease will be summarized by randomization arm, SOC and PT for the Safety Population.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.6.1	Summary of Medical History – Safety Population
15.2.1.7.1	Summary of Concomitant Diseases– Safety Population
LISTINGS	
15.3.1.10	Listing of Medical History and Concomitant Diseases

12.3.4 Other Data

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

- Cotinine urine test.
- Urine pregnancy test.
- Chest x-ray.
- Urine drug screen.
- Serology (excluding HIV status).
- Alcohol breath test.



- Prior medication.
- Willingness to use THS 2.2 Menthol products.
- Product preference question.

Prior Medication will be summarized as described in Section 12.6.4.4.1 “Prior and Concomitant Medication”.

Product preference will be collected at Admission (Day -2) and states the product which the subject prefers to be randomized to (THS 2.2 Menthol, mCC, SA or No preference). Data will be summarized by randomization arms along with Baseline characteristics. Willingness and ability to use the product will be included in the disposition summary table for all screened subjects.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.1	Summary of Subject Disposition – All Screened Subjects
15.2.6.19.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.19.2	Summary of Prior Medication by Preferred Term – Safety Population
LISTINGS	
15.3.1.4	Listing of Product Test and Willingness to Use the Product
15.3.1.6	Listing of Product Preference
15.3.1.7	Listing of Safety Laboratory Entry Criteria
15.3.6.3	Listing of Prior and Concomitant Medication

12.4 Measurements of Product Compliance

From Day -2 onwards during the confinement period, each mCC will be dispensed to the subjects one by one. Subjects in the THS 2.2 Menthol arm will be provided by the site study collaborators with Menthol Tobacco Sticks from Day 1 to Day 5 stick by stick. One mCC/Menthol Tobacco Stick will be allowed at a time.

Levels of CO in exhaled breath will be measured in the SA arm to ensure that the subjects have not smoked any cigarettes. This will serve as a compliance tool starting from Day 2, because of possible carry over effect. These data (continuous and categorical) will be summarized and listed by product use category (Table 20) in the SA arm.

During the ambulatory period, subjects in the 3 study arms will capture, from the time of Discharge on Day 6 to Day 90, the number of product used (e.g., menthol and non-menthol CC, Menthol Tobacco Sticks, or any other tobacco /nicotine-containing products including NRT) on a daily basis in the product use electronic diary. The product use electronic diary will serve as a compliance tool in the 3 arms. On Day 6, the compliance to the product will be ensured using both the accountability log (from 06:30 AM to time



of discharge) and the product use electronic diary (filled from the time of Discharge on Day 6 to Day 90).

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.5.1	Summary of Compliance as Measured by Exhaled CO (ppm) in the SA Arm During Confinement Period- FAS
15.2.5.2	Summary of Compliance by Period - FAS
LISTINGS	
15.3.3.2	Listing of Secondary Biomarkers
15.3.2.1	Listing of Product Usage

12.5 Extent of Exposure (Product Consumption)

Details of the product test prior to enrollment and of product use after randomization will be listed and summarized. During the confinement period the daily usage, as recorded in the log, will be summarized by randomization arm.

The maximum and average daily usage of the assigned product and non-assigned product will be summarized over the whole ambulatory period, as recorded by the subject, and for each of the periods 2 to 4 (see [section 10.2 "Per Protocol Set"](#)).

All summaries will be produced for the Safety Population, and for the PP Set at periods 1 to 4. Summaries of data in Ambulatory will also be repeated for the FAS, if the population differs from the Safety population by more than 10%.

In addition the number and percentage of subjects falling into each product use category (see [Section 6.3.3.1 "Dual-use"](#)) during the ambulatory period will be presented.

The average product use data will also be presented by randomized product and by product use categorization (see [Section 6.3.3.1 "Dual-use"](#)).

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.2.1.1	Summary of Daily Product Use in Confinement Period – Safety Population
15.2.2.1.2	Summary of Daily Product Use in Confinement Period – FAS
15.2.2.1.3	Summary of Daily Product Use in Confinement Period – PP Set
15.2.2.2.1	Summary of Maximum Daily Product Use in Ambulatory Period– Safety Population
15.2.2.2.2	Summary of Maximum Daily Product Use in Ambulatory Period– FAS



TFL number	Title
15.2.2.2.3	Summary of Maximum Daily Product Use in Ambulatory Period– PP Set
15.2.2.3.1	Summary of Average Daily Product Use in Ambulatory Period– Safety Population
15.2.2.3.2	Summary of Average Daily Product Use in Ambulatory Period – FAS
15.2.2.3.3	Summary of Average Daily Product Use in Ambulatory Period – PP Set
15.2.2.4.1	Summary of Product Use by Product Use Category in Ambulatory Period – Safety Population
15.2.2.4.2	Summary of Product Use Category in Ambulatory Period – FAS
15.2.2.4.3	Summary of Product Use Category in Ambulatory Period – PP Set
15.2.2.5.1	Summary of Average Daily Product Use by Product Use Category in Ambulatory Period – Safety Population
15.2.2.5.2	Summary of Average Daily Product Use by Product Use Category in Ambulatory Period – FAS
15.2.2.5.3	Summary of Average Daily Product Use by Product Use Category in Ambulatory Period – PP Set
LISTINGS	
15.3.2.1	Listing of Product Usage
15.3.2.2	Listing of Cigarette Butt and THS Menthol Tobacco Stick Collection Data

12.6 Planned Statistical Analyses

For all statistical analysis data from all arms, THS 2.2 Menthol, mCC and SA will be included in all models as appropriate.

12.6.1 Primary Analyses

12.6.1.1 Analysis of Biomarkers of Exposure for Primary Objectives

The BoExp (COHb in blood and urinary concentrations of MHBMA, 3-HPMA, S-PMA and Total NNAL) used for the primary analysis will be described as detailed in [Section 12.1.3 “Descriptive Statistics”](#). The listing of the COHb data will have a flag for whether a subject’s COHb was <2%.

The baseline is as defined in [Section 12.1.4 “Definitions for Statistical Data Analysis”](#).

The primary endpoints will be log-transformed (base_e) prior to analysis. The analysis will compare the evening COHb level (20:00-21:30) at Day 5; and urinary concentrations of MHBMA, 3-HPMA and S-PMA adjusted for creatinine on Day 5 and urinary concentrations of Total NNAL adjusted for creatinine on Day 90 Visit between the THS 2.2 Menthol and mCC arms for the PP Set. An analysis of covariance (ANCOVA) ([Snedecor and Cochran 1982](#)) model will be used with terms for the log-transformed baseline value, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm.



The SAS code to be used for the THS 2.2 Menthol and mCC data is shown below:

```
Proc glm data=_data_ ;
Class randomization_arm sex cigarette_cons;
Model log biomarker = log_baseline sex cigarette_cons
randomization_arm;
Lsmean randomization_arm / pdiff =control('mCC') alpha=0.05 cl;
Run;
```

The least squares (LS) means and estimate of the difference and the 95% CI will be back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), two-sided 95% CI and one-sided p-value will be presented in the tables. THS 2.2 Menthol : CC effects will be graphed in a forest plot.

All figures, summaries and analyses will be performed on the PP Set. Additional descriptive statistics will be provided within the secondary analysis.

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.1.1	Forest Plots of Statistical Analysis of Biomarkers of Exposure for Primary Objective – PP Set
15.1.1.2	Biomarker of Exposure for Primary Objective Arithmetic Mean and 95% CI for Percent Change from Baseline – PP Set
TABLES	
15.2.3.1.1	Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective – PP Set
15.2.4.1.1	Descriptive Statistics of Blood COHb (%) – PP Set
15.2.4.1.1.1	Descriptive Statistics of Blood COHb (%) by Sex – PP Set
15.2.4.1.1.2	Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – PP Set
15.2.4.2.1	Descriptive Statistics of MHBMA in 24-hour Urine Collection – PP Set
15.2.4.2.1.1	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set
15.2.4.2.1.2	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set
15.2.4.3.1	Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – PP Set
15.2.4.3.1.1	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set



TFL number	Title
15.2.4.3.1.2	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set
15.2.4.4.1	Descriptive Statistics of S-PMA in 24-hour Urine Collection – PP Set
15.2.4.4.1.1	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set
15.2.4.4.1.2	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set
15.2.4.5.1	Descriptive Statistics of Total NNAL in 24-hour Urine Collection – PP Set
15.2.4.5.1.1	Descriptive Statistics of Total NNAL Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Sex – PP Set
15.2.4.5.1.2	Descriptive Statistics of Total NNAL Urinary Concentration Adjusted for Creatinine (units) in 24-hour Urine Collection by Cigarette Consumption – PP Set
	LISTINGS
15.3.3.1.1	Listing of Biomarkers of Exposure COHb and CO.
15.3.3.1.2	Listing of Biomarkers of Exposure MHBMA and 3-HPMA.
15.3.3.1.3	Listing of Biomarkers of Exposure S-PMA and Total NNAL..

12.6.1.2 Confirmatory Analysis

The hypothesis to be tested is that the geometric mean level of the BoExp for THS 2.2 Menthol is lower relative to mCC and will be as described in [Section 12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Objectives"](#).

12.6.1.3 Sensitivity Analysis

As a sensitivity analysis, the ANCOVA model described in [Section 12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Objectives"](#) will be repeated for the PP Set at Day 5 and Day 90 data by means of a mixed model approach, without the LOCF data imputation described in [Section 12.1.5 "Handling of Dropouts or Missing Data \(including outside the limits of quantification\)"](#). Any data outside of the allowed time window (see [Table 18: Assessment Windows](#)) on Days 5 and 90 will be excluded from the analysis.



The SAS code to be used for the THS 2.2 Menthol and mCC data is shown below:

```
Proc mixed data= data_;
Class randomization_arm sex cigarette_cons;
Model log biomarker = log_baseline sex cigarette_cons
randomization_arm;
Lsmean randomization_arm / pdiff =control('mCC') alpha=0.05 cl;
Run;
```

An additional sensitivity analysis will be produced for the primary analysis, summaries and graphs of the COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL will be repeated for the compliant population for THS 2.2 Menthol vs mCC. The analysis will use the same model as described in [Section 12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Objectives"](#)

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.1.3	Biomarker of Exposure Arithmetic Mean and 95% CI for Percent Change from Baseline – Compliant Population
TABLES	
15.2.3.1.2	Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective using Mixed Model – PP Set
15.2.3.1.3	Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective – Compliant Population
15.2.4.1.3	Descriptive Statistics of Blood COHb (%) – Compliant Population
15.2.4.2.3	Descriptive Statistics of MHBMA in 24-hour Urine Collection – Compliant Population
15.2.4.3.3	Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – Compliant Population
15.2.4.4.3	Descriptive Statistics of S-PMA in 24-hour Urine Collection – Compliant Population
15.2.4.5.3	Descriptive Statistics of Total NNAL in 24-hour Urine Collection – Compliant Population

12.6.2 Secondary Analyses

The analysis of COHb, MHBMA, 3-HPMA, and S-PMA at Day 90 and Total NNAL at Day 5 will be repeated for the PP Set.

The analysis of the COHb, MHBMA, 3-HPMA, S-PMA at Day 5/ Day 90 and Total NNAL at Day 90 will be repeated for the FAS as described in [Section 12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Objectives"](#). These endpoints will also be



examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as for the primary analysis for the PP Set.

The baseline is for the biomarkers measured in urine is as defined in [Section 12.1.4 "Definitions for Statistical Data Analysis"](#).

12.6.2.1 Analysis of Biomarkers of Exposure for Secondary Objectives

The BoExp for the secondary objectives are exhaled CO and total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA and NEQ (all analysed from a 24-hour urine collection) at Day 5 and Day 90 will be described as reported in [Section 12.1.3 "Descriptive Statistics"](#). Urine parameters will be analyzed as concentration adjusted for creatinine and the quantity excreted in urine over 24 hours. In addition the quantity excreted in urine over 24 hours for MHBMA, 3-HPMA, S-PMA and Total NNAL will also be presented as above.

All BoExp apart from CO breath test will be analyzed in the log scale.

BoExp will be analyzed using the same model described in [Section 12.6.1.1 "Analysis of Biomarkers of Exposure for Primary Objectives"](#). No adjustment will be made for multiple comparisons. For all BoExp, if the results from the Day 5 analysis are significant (one-sided p-value ≤ 0.025) then the statistical significance will be evaluated for the results of the analysis at Day 90 values. LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables. Forest plots of the ratios and 95% CI will also be produced.

BoExp will also be examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as above for the PP Set. In addition, the sensitivity analyses described in [Section 12.6.1.3 "Sensitivity Analysis"](#) for the biomarkers of exposure for primary objectives will be repeated for the biomarkers of exposure for secondary objectives.

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.1.2	Biomarker of Exposure Arithmetic Mean and 95% CI for Percent Change from Baseline – PP Set
15.1.1.4	Biomarker of Exposure Arithmetic Mean and 95% CI for Percent Change from Baseline – FAS
15.1.1.5	Forest Plots of Statistical Analysis of Biomarkers of Exposure for Secondary Objective – PP Set
TABLES	
15.2.3.2	Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5/90 Visit versus mCC and SA for the Secondary Objective – PP Set.



TFL number	Title
15.2.3.3	Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5/90 Visit versus mCC and SA for the Secondary Objective – FAS.
15.2.3.4	Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit– PP Set.
15.2.3.5	Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit– FAS.
15.2.3.6	Analysis of Additional Biomarkers of Exposure versus mCC and SA using Mixed Model on Day 5/90 Visit – PP Set
15.2.3.7	Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit– Compliant Population
15.2.4.1.2	Descriptive Statistics of Blood COHb (%) – FAS
15.2.4.1.3	Descriptive Statistics of Blood COHb (%) – Compliant Population
15.2.4.2.2	Descriptive Statistics of MHBMA in 24-hour Urine Collection – FAS
15.2.4.2.3	Descriptive Statistics of MHBMA in 24-hour Urine Collection – Compliant Population
15.2.4.3.2	Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – FAS
15.2.4.3.3	Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – Compliant Population
15.2.4.4.2	Descriptive Statistics of S-PMA in 24-hour Urine Collection – FAS
15.2.4.4.3	Descriptive Statistics of S-PMA in 24-hour Urine Collection – Compliant Population
15.2.4.5.2	Descriptive Statistics of Total NNAL in 24-hour Urine Collection – FAS
15.2.4.5.3	Descriptive Statistics of Total NNAL in 24-hour Urine Collection – Compliant Population
15.2.4.6.1	Descriptive Statistics of Exhaled CO (ppm) – PP Set
15.2.4.6.2	Descriptive Statistics of Exhaled CO (ppm) – FAS
15.2.4.7.1	Descriptive Statistics of 1-OHP in 24-hour Urine Collection – PP Set
15.2.4.7.2	Descriptive Statistics of 1-OHP in 24-hour Urine Collection – FAS
15.2.4.8.1	Descriptive Statistics of Total NNN in 24-hour Urine Collection – PP Set
15.2.4.8.2	Descriptive Statistics of Total NNN in 24-hour Urine Collection – FAS
15.2.4.9.1	Descriptive Statistics of 4-ABP in 24-hour Urine Collection – PP Set
15.2.4.9.2	Descriptive Statistics of 4-ABP in 24-hour Urine Collection – FAS
15.2.4.10.1	Descriptive Statistics of 1-NA in 24-hour Urine Collection – PP Set
15.2.4.10.2	Descriptive Statistics of 1-NA in 24-hour Urine Collection – FAS
15.2.4.11.1	Descriptive Statistics of 2-NA in 24-hour Urine Collection – PP Set
15.2.4.11.2	Descriptive Statistics of 2-NA in 24-hour Urine Collection – FAS
15.2.4.12.1	Descriptive Statistics of o-tol in 24-hour Urine Collection – PP Set
15.2.4.12.2	Descriptive Statistics of o-tol in 24-hour Urine Collection – FAS
15.2.4.13.1	Descriptive Statistics of CEMA in 24-hour Urine Collection – PP Set
15.2.4.13.2	Descriptive Statistics of CEMA in 24-hour Urine Collection – FAS
15.2.4.14.1	Descriptive Statistics of HEMA in 24-hour Urine Collection – PP Set
15.2.4.14.2	Descriptive Statistics of HEMA in 24-hour Urine Collection – FAS
15.2.4.15.1	Descriptive Statistics of B[a]P in 24-hour Urine Collection – PP Set



TFL number	Title
15.2.4.15.2	Descriptive Statistics of B[a]P in 24-hour Urine Collection – FAS
15.2.4.16.1	Descriptive Statistics of HMPMA in 24-hour Urine Collection – PP Set
15.2.4.16.2	Descriptive Statistics of HMPMA in 24-hour Urine Collection – FAS
15.2.4.17.1	Descriptive Statistics of S-BMA in 24-hour Urine Collection – PP Set
15.2.4.17.2	Descriptive Statistics of S-BMA in 24-hour Urine Collection – FAS
15.2.4.18.1	Descriptive Statistics of NEQ in 24-hour Urine Collection – PP Set
15.2.4.18.2	Descriptive Statistics of NEQ in 24-hour Urine Collection – FAS
LISTINGS	
15.3.3.2.1	Listing of Biomarkers of Exposure (total 1-OHP and total NNN)
15.3.3.2.2	Listing of Biomarkers of Exposure (4-ABP and 1-NA)
15.3.3.2.3	Listing of Biomarkers of Exposure (2-NA and o-tol)
15.3.3.2.4	Listing of Biomarkers of Exposure (CEMA and HEMA)
15.3.3.2.5	Listing of Biomarkers of Exposure (B[a]P and HMPMA)
15.3.3.2.6	Listing of Biomarkers of Exposure (S-BMA and NEQ)

12.6.2.2 Nicotine and Cotinine Concentrations

The concentrations of nicotine and cotinine will be listed and summarized. During confinement, the evening concentration levels at 08:00 PM is considered. Baseline is the assessment at 08:00 PM to 09:30 PM on Day 0. Line graphs of the nicotine and cotinine concentration profiles across all study days showing mean and 95% CI of percent change from baseline will also be produced.

Nicotine and cotinine concentrations at each post-baseline timepoint will be analysed in the log space using an ANCOVA model with terms for log-transformed baseline concentration, sex, average daily mCC consumption over the last 4 weeks as reported during screening, time point, product, and the interaction term between time point and product. No adjustment will be made for multiple comparisons.

The SAS code described in Section 12.6.1.3 "Sensitivity Analysis" will be used for the analysis of nicotine and cotinine.

Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the PP Set and FAS by randomization arm.

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.2.1.1	Plasma Nicotine and Cotinine Profile (ng/mL) over the 90 Days Arithmetic Mean and 95% CI for Percent change from baseline – PP Set



TFL number	Title
15.1.2.1.2	Plasma Nicotine and Cotinine Profile (ng/mL) over the 90 Days Arithmetic Mean and 95% CI for Percent change from baseline – FAS
TABLES	
15.2.4.19.1	Descriptive Statistics of Plasma Nicotine and Cotinine Concentrations (ng/mL) – PP Set
15.2.4.19.2	Descriptive Statistics of Plasma Nicotine and Cotinine Concentrations (ng/mL) – FAS
15.2.4.20.1	Analysis of Plasma Nicotine and Cotinine Concentrations (ng/mL) over the 90 Days – PP Set
15.2.4.20.2	Analysis of Plasma Nicotine and Cotinine Concentrations (ng/mL) over the 90 Days – FAS
LISTINGS	
15.3.3.3	Listing of Plasma Nicotine and Cotinine Concentrations

12.6.2.3 Nicotine and Cotinine Pharmacokinetic Parameters

The parameters C_{peak} , C_{avg} and t_{peak} will be calculated on Day 5 as described in [Section 7.2 "Pharmacokinetic Parameters"](#). The data will be listed and summarized for both nicotine and cotinine.

The analysis will compare the log-transformed C_{peak} and C_{avg} on Day 5 between the THS 2.2 Menthol and mCC arms. An analysis of variance (ANOVA) model will be used with terms for sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm.

The SAS code will be similar to that described in [Section 12.6.1.3 "Sensitivity Analysis"](#), with no baseline value being included in the model.

LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables.

For t_{peak} on Day 5 the comparison between the THS 2.2 Menthol and mCC arms will be made by the Wilcoxon Rank Sum test using PROC NPARIWAY in SAS. Median difference and 95% CI using the Hodges-Lehmann estimate will be tabulated.

The following code will be used:

```
Proc npariway data= data_h1 median;
Class randomization_arm;
Var tpeak;
Run;
```

All summaries and analyses will be performed on the PP Set and FAS.

The data will be presented in the below outputs:



TFL number	Title
TABLES	
15.2.4.21.1	Descriptive Statistics of Plasma Nicotine and Cotinine PK Parameters on Day 5 – PP Set
15.2.4.21.2	Descriptive Statistics of Plasma Nicotine and Cotinine PK Parameters on Day 5 – FAS
15.2.4.22.1	Analysis of Plasma Nicotine and Cotinine PK Parameters on Day 5 – PP Set
15.2.4.22.2	Analysis of Plasma Nicotine and Cotinine PK Parameters on Day 5 – FAS
LISTINGS	
15.3.3.4	Listing of Nicotine and Cotinine PK Parameters on Day 5

12.6.2.4 CYP1A2 Activity

CYP1A2 activity will be measured in plasma on Day 0, Day 5 and Day 90. In this study the CYP1A2 activity will be calculated using the molar ratio of PX and CAF, as described in [Section 7.1.3 "CYP1A2"](#). Descriptive statistics of the values and percent change on Days 5 and 90 from Baseline and supportive listings will be provided.

The analysis will compare the log-transformed Day 5 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms. ANCOVA models will be used on CYP1A2 activity levels with terms for log-transformed baseline, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm. No adjustment will be made for multiple comparisons. If the results from the Day 5 analysis are significant (one-sided p-value ≤ 0.025) then the statistical significance will be repeated for the analysis at the Day 90 values. The SAS code will be similar to that described in [Section 12.6.1.3 "Sensitivity Analysis"](#).

Geometric LS means for each product along with the ratio (THS 2.2 Menthol :mCC) and 95% CI will be presented in the tables.

CYP1A2 activity will also be examined to compare the observed reductions in THS 2.2 Menthol vs. SA using the same methodology as above.

If there are any CYP1A2 assessments performed within 5 half-lives since the use of a concomitant medication affecting CYP1A2 activity, the analysis will be repeated by excluding these assessments for both the PP Set and FAS

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.23.1	Descriptive Statistics of CYP1A2 Activity (%) – PP Set
15.2.4.23.2	Descriptive Statistics of CYP1A2 Activity (%) – FAS



TFL number	Title
15.2.4.24.1	Analysis of CYP1A2 Activity (%) – PP Set
15.2.4.24.2	Analysis of CYP1A2 Activity (%) – FAS
LISTINGS	
15.3.3.5	Listing of CYP1A2 Activity and Changes from Baseline

12.6.2.5 Risk Markers

The risk markers are:

- Systolic and diastolic blood pressure on Day 0, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, and TC in serum on Day 0, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Fibrinogen in plasma on Day 0, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- HbA1c in blood on Day 0 and Day 90 Visit.
- sICAM-1 in serum on Day 0, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- WBC and platelet count in blood on Day 0, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-PGF2 α and 11-DTX-B2 in 24 hour urine on Day 0, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
- Body weight and waist circumference on Day -2 and Day 90 Visit.

The results along with the changes from baseline will be listed and summarized. In addition line graphs will be produced for product means (and 95% CI) over all timepoints.

The analysis will compare the results on Day 90 between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms for the FAS and PP set. An ANCOVA model will be used with terms for Baseline, sex, average daily mCC consumption over the last 4 weeks as reported during screening and randomization arm. No adjustment will be made for multiple comparisons.

Blood pressure, HbA1c, LDL, HDL, TG, TC, WBC, body weight and waist circumference will be analyzed in the regular scale. 8-epi-PGF2 α , 11-DTX-B2, sICAM will be analyzed in the logarithmic scale. Other risk markers will be logarithmically transformed prior to analysis if there is evidence of non-normality by means of Shapiro-Wilks test.

The SAS code will be the same as described in [Section 12.6.1.1 “Analysis of Biomarkers of Exposure for Primary Objectives”](#).



LS means for each product along with the difference (THS 2.2 Menthol - mCC) or ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables along with a forest plot of the results.

If there are any 11-DTX-B2 assessments performed within 5 half-lives since the use of a concomitant medication affecting the production of 11-DTX-B2, the analysis will be repeated by excluding these assessments for both the PP Set and FAS

All tables, figures and analyses will be produced for the FAS and PP set. Figures will be produced for the PP Set.

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.2.3.1	Forest Plot of Statistical Analysis of Risk Markers – PP Set
15.1.2.4.1	Risk Markers Arithmetic Mean and 95% CI for Percent change from baseline – PP Set
15.1.2.4.2	Risk Markers Arithmetic Mean and 95% CI for Percent change from baseline – FAS
TABLES	
15.2.4.25.1	Statistical Analysis of Risk Markers – PP Set
15.2.4.25.2	Statistical Analysis of Risk Markers – FAS
15.2.4.26.1	Descriptive Statistics of Blood Pressure (mmHg) – PP Set
15.2.4.26.2	Descriptive Statistics of Blood Pressure (mmHg) – FAS
15.2.4.27.1	Descriptive Statistics of hs-CRP (units), homocysteine (units), blood glucose (units), LDL (units), HDL (units), TG (units), and TC (units) – PP Set
15.2.4.27.2	Descriptive Statistics of hs-CRP (units), homocysteine (units), blood glucose (units), LDL (units), HDL (units), TG (units), and TC (units) – FAS
15.2.4.28.1	Descriptive Statistics of Fibrinogen (units) – PP Set
15.2.4.28.2	Descriptive Statistics of Fibrinogen (units) – FAS
15.2.4.29.1	Descriptive Statistics of HbA1c (units) – PP Set
15.2.4.29.2	Descriptive Statistics of HbA1c (units) – FAS
15.2.4.30.1	Descriptive Statistics of sICAM (units) – PP Set
15.2.4.30.2	Descriptive Statistics of sICAM (units) – FAS
15.2.4.31.1	Descriptive Statistics of Total WBC Count (units), Neutrophils Counts (units), Basophils Counts (Units), Eosinophils Counts (units), Lymphocytes Counts (units), Monocytes Counts (units) and Platelet Count (units) – PP Set
15.2.4.31.2	Descriptive Statistics of Total Total WBC Count (units), Neutrophils Counts (units), Basophils Counts (Units), Eosinophils Counts (units), Lymphocytes Counts (units), Monocytes Counts (units) and Platelet Count (units) – FAS



TFL number	Title
15.2.4.32.1	Descriptive Statistics of 8-epi-PGF2 α (units) and 11-DTX-B2 (units) – PP Set
15.2.4.32.2	Descriptive Statistics of 8-epi-PGF2 α (units) and 11-DTX-B2 (units) – FAS
15.2.4.33.1	Descriptive Statistics of Body weight (kg) and waist circumference (cm) – PP Set
15.2.4.33.2	Descriptive Statistics of Body weight (kg) and waist circumference (cm) – FAS
LISTINGS	
15.3.3.5	Listing of Risk Markers and Collection Times

12.6.3 Exploratory Analysis

12.6.3.1 Questionnaires

12.6.3.1.1 FTND Questionnaire

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

FTND score value and the number and percentage of subjects in each category (mild/moderate/severe) will be presented at Screening and Day 90 Visit. The percent change from Baseline in the FTND score at Day 90 will also be presented. The changes in the categories will also be presented in a shift table.

All summaries and shift tables will be performed on the PP, FAS and Compliant populations.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – PP Set
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – PP Set
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set
15.2.4.34.1	Summary of Fagerström Test for Nicotine Dependence Results – PP Set
15.2.4.34.2	Summary of Fagerström Test for Nicotine Dependence Results – FAS



TFL number	Title
15.2.4.34.3	Summary of Fagerström Test for Nicotine Dependence Results – Compliant Population
LISTINGS	
15.3.6.11	Listing of Fagerström Test for Nicotine Dependence Results

12.6.3.1.2 Urge-to-Smoke Questionnaire of Smoking Urges Brief

The QSU-brief will be administered daily from Days -1 to 5, and Days 30, 60 and 90. The change from baseline will be calculated for the total score and the two domain scores (relief and reward). The total score and two domain scores, along with the percent change from baseline will be summarized. The answers to the individual questions, along with the domain scores, total scores, changes and percent changes from baseline will be listed.

The profiles of the raw means from baseline to Day 90 Visit for the total score and two domain scores will be produced.

The analysis will be performed separately for each post-baseline timepoint in the domain and total scores. An ANCOVA model will be used with terms for baseline QSU-BRIEF score, sex, average daily mCC consumption over the last 4 weeks as reported during screening, and randomization arm. No adjustment will be made for multiple comparisons. The SAS code to be used is similar to the model reported in Section 12.6.1.3 "Sensitivity Analysis", amended as appropriate to obtain the required comparisons.

LS means for each randomization arm along with the difference (THS 2.2 Menthol - mCC) and (THS 2.2 Menthol - SA) with 95% CI will be presented in the tables.

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

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.2.12.1	QSU-brief Total Scores and Percent Change Mean and 95% CI – PP Set
15.1.2.12.2	QSU-brief Total Scores and Percent Change Mean and 95% CI – FAS
15.1.2.13.1	QSU-brief Total Scores Least Squares Means Differences and 95% CI – PP Set
15.1.2.13.2	QSU-brief Total Scores Least Squares Means Differences and 95% CI – FAS
TABLES	
15.2.4.35.1	Descriptive Statistics of QSU-brief Factors and Total Scores – PP Set
15.2.4.35.2	Descriptive Statistics of QSU-brief Factors and Total Scores – FAS
15.2.4.36.1	Analysis of QSU-brief Factors and Total Scores – PP Set
15.2.4.36.2	Analysis of QSU-brief Factors and Total Scores – FAS



TFL number	Title
LISTINGS	
15.3.6.12	Listing of QSU-brief Questionnaire Results

12.6.3.1.3 Modified Cigarette Evaluation Questionnaire

The mCEQ will be administered daily from Days -1 to 5, and Days 30 Visit, 60 Visit and 90 Visit. All summaries, profiles and analysis will be presented for the THS 2.2 Menthol and mCC only. The mCEQ is not captured for the SA arm.

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

The profiles of the raw means from baseline to Day 90 for the five subscale scores will be produced.

The analysis will be performed separately for each post-baseline timepoint in the subscales. An ANCOVA model will be used with terms for baseline mCEQ score, sex, and average daily mCC consumption over the last 4 weeks as reported during screening. No adjustment will be made for multiple comparisons.

The SAS code to be used is similar to the model reported in Section 12.6.1.3 "Sensitivity Analysis".

LS means for each product along with the difference (THS 2.2 Menthol - mCC) with 95% CI will be presented in the tables.

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

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.2.14.1	MCEQ Subscales Mean and 95% CI of Percent Change from Baseline– PP Set
15.1.2.14.2	MCEQ Subscales Mean and 95% CI of Percent Change from Baseline – FAS
15.1.2.15.1	MCEQ Subscales Least Squares Means Differences and 95% CI – PP Set
15.1.2.15.2	MCEQ Subscales Least Squares Means Differences and 95% CI – FAS
TABLES	
15.2.4.37.1	Descriptive Statistics of MCEQ Subscales – PP Set
15.2.4.37.2	Descriptive Statistics of MCEQ Subscales – FAS
15.2.4.38.1	Analysis of MCEQ Subscales – PP Set
15.2.4.38.2	Analysis of MCEQ Subscales – FAS



TFL number	Title
LISTINGS	
15.3.6.14	Listing of MCEQ Questionnaire Results and Changes from Baseline

12.6.3.1.4 Minnesota Nicotine Withdrawal Questionnaire

The MNWS will be administered daily from Days 0 to 6, and Days 31, 61 and 91 for the assessment of Day-1 to Day 5, and Days 30, 60 and 90 as it is a 24-hour recall questionnaire.

All summaries, profiles and analysis will be presented for the day before the assessment in the THS 2.2 Menthol, mCC and SA arms.

The total score, along with the percent change from baseline will be summarized. The answers to the individual questions, along with the total score, the changes and percent changes from baseline will be listed.

The profiles of the raw means from baseline to Day 90 for the total score will be plotted.

The analysis will compare each post baseline timepoint separately for the total score. An ANCOVA model will be used with terms for baseline score, sex, and average daily mCC consumption over the last 4 weeks as reported during screening. No adjustment will be made for multiple comparisons.

The SAS code to be used is similar to the model reported in Section 12.6.1.3 "Sensitivity Analysis".

LS means for each product along with the difference (THS 2.2 Menthol - mCC) and (THS 2.2 Menthol - SA) with 95% CI will be presented in the tables.

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

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.2.16.1	MNWS Total Score Mean and 95% CI of Percent Change from Baseline- PP Set
15.1.2.16.2	MNWS Total Score Mean and 95% CI of Percent Change from Baseline - FAS
15.1.2.17.1	MNWS Total Score Arithmetic Least Squares Means and 95% CI - PP Set
15.1.2.17.2	MNWS Total Score Arithmetic Least Squares Means and 95% CI - FAS
TABLES	
15.2.4.39.1	Descriptive Statistics of MNWS Total Score - PP Set
15.2.4.39.2	Descriptive Statistics of MNWS Total Score - FAS



TFL number	Title
15.2.4.40.1	Analysis of MNWS Total Score – PP Set
15.2.4.40.2	Analysis of MNWS Total Score – FAS
LISTINGS	
15.3.6.13	Listing of MNWS Questionnaire Results

12.6.3.1.5 Human Smoking Topography Questionnaire

The HST questionnaire will be administered on Days 0, 4, 30, 60 and 90.

The number and percentage of subjects in each category of the items of the questionnaire will be summarized. The individual responses will be listed.

All summaries will be performed on the FAS.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.41	Descriptive Statistics of HST Questionnaire Data – FAS
LISTINGS	
15.3.7.2	Listing of HST Questionnaire Results

12.6.3.2 Human Smoking Topography Parameters

The HST assessments will take place on Day 0, Day 1, Day 4, Day 30, Day 60 and Day 90 in the THS 2.2 Menthol and mCC arms only, if mCC are compatible with the HST SODIM® device. On Day 0, Day 1 and Day 4 the HST will be conducted on each product use. On Day 30, Day 60 and Day 90 the HST will be recorded over a 4-hour period only.

The per puff parameters are shown in [Table 8](#) and the per cigarette parameters are shown in [Table 9](#).

The per-cigarette parameters derived from the HST assessments will be averaged per day and summarized along with their changes from baseline. The per-puff and per-cigarette parameters will be listed. In addition the randomization arm mean and 95% CI per cigarette parameters will be presented graphically.

The averaged per-cigarette parameters will be analysed on Days 1, 4, 30, 60 and 90 separately using an ANCOVA model with terms for baseline score, sex, average daily mCC consumption over the last 4 weeks as reported during screening, and randomization arm. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in [Section 12.6.1.3 "Sensitivity Analysis"](#).



LS means for each product along with the difference (THS 2.2 Menthol - mCC) and 95% CI will be presented in the tables.

All figures, summaries and analyses will be performed on the FAS by product and product use categories.

The data will be presented in the below outputs:

TFL number	Title
FIGURES	
15.1.2.18	HST per Cigarette Parameters Mean and 95% CI of Percent Change from Baseline by product use category – FAS
TABLES	
15.2.4.42	Descriptive Statistics of HST Parameters per Cigarette – FAS
15.2.4.43	Analysis of HST Parameters per Cigarette – FAS
LISTINGS	
15.3.7.1	Listing of HST Assessments and Changes from Baseline

12.6.3.3 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Day 0, Day 6 and Day 91. In this study the CYP2A6 activity will be calculated using the metabolic ratio of trans 3' hydroxycotinine and cotinine, as described in Section 7.1.4 "CYP2A6". Descriptive statistics of the values and percent change on Days 6 and 91 from Baseline and supportive listings will be provided.

The analysis will compare the log-transformed Day 6 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms.. ANCOVA models will be used with terms for log-transformed baseline, sex, average daily mCC consumption over the last 4 weeks as reported during screening and study arm. No adjustment will be made for multiple comparisons. If the results from the Day 6 analysis are significant (one-sided p-value ≤ 0.025) then the statistical significance will be repeated for the analysis at the Day 91 values. The SAS code will be similar to that described in [Section 12.6.1.3 "Sensitivity Analysis"](#).

Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI will be presented in the tables

CYP2A6 activity will also be examined to compare the reductions in THS 2.2 Menthol vs. SA using the same methodology as above.

If there are any CYP2A6 assessments performed within 5 half-lives since the use of a concomitant medication affecting CYP2A6 activity, the analysis will be repeated by excluding these assessments for both the PP Set and FAS

All summaries and analyses will be performed on the FAS and PP Set.



The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.44.1	Descriptive Statistics of CYP2A6 Activity (%) – PP Set
15.2.4.44.2	Descriptive Statistics of CYP2A6 Activity (%) – FAS
15.2.4.45.1	Analysis of CYP2A6 Activity – PP Set
15.2.4.45.2	Analysis of CYP2A6 Activity – FAS
LISTINGS	
15.3.6.16	Listing of CYP2A6 Activity and Changes from Baseline

12.6.3.4 Relationship between BoExp and NEQ

The analysis of the relationship between NEQ and primary and secondary BoExp will be reported in a separate report as stated in [Section 9 “CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS”](#).

12.6.3.5 Relationship Between Risk Markers and NEQ

The analysis of the relationship between risk markers and NEQ will be reported in a separate report as stated in [Section 9 “CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS”](#).

12.6.3.6 Ames Mutagenicity Test

The 24 hour urine collection for the Ames mutagenicity test will be on Day 0, Day 5 and Day 90.

Descriptive statistics of the values and percent changes on Day 5 and Day 90 from Baseline of the YG1024+S9 mutagenicity will be provided, along with listings.

All summaries will be performed on the FAS, and PP Set.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.46.1	Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (units) – PP Set
15.2.4.46.2	Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (units) – FAS
LISTINGS	
15.3.5.1	Listing of Mutagenicity Results



12.6.3.7 Visual Inspection of the Tobacco Plugs

The collection of the tobacco plugs from the THS 2.2 Menthol products will be performed on Days 1 to 5, and Days 30, 60 and 90. The number and percentage of tobacco plugs showing each of the following criteria will be summarized by day: "Ashes not anymore visible when shooting picture"; "No tobacco in plug"; "Not enough tobacco in the plug to perform the analysis"; "Tobacco plug destroyed, analysis impossible"; "No tobacco plug in the vial"; "Other error".

All summaries will be performed on the FAS only.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.47	Descriptive Statistics of Visual Inspection of the THS 2.2 Menthol Tobacco Plugs Data – FAS
LISTINGS	
15.3.6.17	Listing of Visual Inspection of the Tobacco Plugs

12.6.3.8 Filter Analysis

The filter analysis from the THS 2.2 products will be performed from Days 1 to 5. Descriptive statistics will be provided for smoke nicotine in filter and UV absorbance at 310 nm along with listings.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.48	Descriptive Statistics of Filter Analysis from the THS 2.2 Menthol Products – FAS
LISTINGS	
15.3.6.18	Listing of Filter Analysis Data

12.6.3.9 Product preference analysis

The product preference as asked at admission will serve as a sensitivity analysis for the product exposure.

All summaries will be produced for the FAS.

These data will also be presented categorized separately by product preference and by product use categorization during periods 2-4 (see [Section 6.3.3.1 "Dual-use"](#)).



The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.49	Summary of Average Daily Product Use in Ambulatory Period by Preferred Product Declared at Admission – FAS
15.2.4.50	Summary of Product Use Categories by Preferred Product Declared at Admission – FAS

12.6.4 Safety Evaluation

Safety variables monitored in this study include: AEs; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; concomitant medication, clinical chemistry, hematology, urine analysis safety panel, BMI, physical examination, respiratory symptoms (cough assessment).

12.6.4.1 Safety Reporting

The primary analysis of Safety parameters will be conducted on the Safety population as described in [Section 12.1.3 “Descriptive statistics”](#). AE and laboratory findings summaries will be produced also for the Full Safety population.

12.6.4.2 Adverse Events

A product emergent AE is defined as an AE that occurs after first product use or that is present prior to first product use and becomes more severe after first product use. All other AEs will not be summarized but provided in listings only.

All AEs occurring from the signing of informed consent will be recorded electronically. However, only product emergent AEs will be summarized. The AE listings will include all AEs captured in the database at any time during the study (including those from subjects who were not in the safety population).

In general, AE summary tables reporting the number of events and the number and percentage of subjects reporting at least one AE will be produced by study arm for the Pre-Randomization and Randomized periods, as reported in [Section 12.6.4.1 “Safety Reporting”](#). AE data during the Randomized period will also be presented stratified by Confinement, Ambulatory, and Safety Follow-up.

Ambulatory AE data will also be reported by product use category (see [Table 20](#)) defined on product use over the whole ambulatory period. In particular, the general product use categories for THS 2.2 will be used, and the [Predominantly Abstinence] and [Smoking Abstinence] categories will be presented for THS 2.2 Menthol and mCC arm if at least one subject is associated to these categories.



12.6.4.2.1 All Adverse Events

A general summary table of AEs will be presented including:

- The number of events and the number and percentage of subjects reporting at least one AE.
- The number of events and the number and percentage of subjects reporting at least one study product-related AE, broken down by product relatedness (related to THS 2.2 Menthol / mCC) and expectedness (expected for THS 2.2 Menthol / mCC).
- The number of events and the number and percentage of subjects reporting at least one AE broken down by severity including each subject only once with his worst severity.
- The number of events and the number and percentage of subjects reporting at least one SAE.
- The number of events and the number and percentage of subjects reporting at least one AE leading to any action taken, broken down by action taken related to the product (product use interrupted, product use reduced, product use stopped, not applicable, none), treatment given (yes, no), study discontinuation, other action taken.
- The number of events and the number and percentage of subjects reporting at least one AE related to study procedure

Additional summary tables of AEs will be presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by SOC and PT coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 16.0 or later).

If a subject has more than one occurrence of the same AE, the subject will be counted only once within a PT with the worst occurrence based on the presentation (e.g., for presentation by severity = most severe, for presentation by relationship = most related). Missing information on the intensity of AE will be counted as severe.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.1.1	Summary of Adverse Events– Safety Population
15.2.6.1.2	Summary of Adverse Events– Full Safety Population
15.2.6.2.1	Summary of Adverse Events by Product Use Category in Ambulatory – Safety Population



TFL number	Title
15.2.6.2.2	Summary of Adverse Events by Product Use Category in Ambulatory – Full Safety Population
15.2.6.3.1	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.3.2	Summary of Adverse Events by System Organ Class and Preferred Term – Full Safety Population
15.2.6.4.1	Summary of Adverse Events by Product Use Category, System Organ Class and Preferred Term – Safety Population
15.2.6.4.2	Summary of Adverse Events by Product Use Category, System Organ Class and Preferred Term – Full Safety Population
15.2.6.5.1	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.5.2	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Full Safety Population
15.2.6.6.1	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.6.2	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Full Safety Population
15.2.6.7.1	Summary of Adverse Events Leading to Study Product Discontinuation, Interruption, or Reduction by System Organ Class and Preferred Term – Safety Population
15.2.6.7.2	Summary of Adverse Events Leading to Study Product Discontinuation, Interruption, or Reduction by System Organ Class and Preferred Term – Full Safety Population
15.2.6.8.1	Summary of Adverse Events Leading to Study Product Discontinuation, Interruption, or Reduction by Product Use Category, System Organ Class, and Preferred Term – Safety Population
15.2.6.8.2	Summary of Adverse Events Leading to Study Product Discontinuation, Interruption, or Reduction by Product Use Category, System Organ Class, and Preferred Term – Full Safety Population
15.2.6.9.1	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population
15.2.6.9.2	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Full Safety Population
15.2.6.10.1	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.10.2	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Full Safety Population
15.2.6.11.1	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Severity – Safety Population



TFL number	Title
15.2.6.11.2	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Severity – Full Safety Population
LISTINGS	
15.3.6.1.1	Listing of Adverse Events

12.6.4.2.2 Serious Adverse Events (Including Deaths)

A summary table of SAEs will be presented using the same approach as for AEs (see [Section 12.6.4.2 “Adverse Events”](#)), and including the number of events and the number and percentage of subjects reporting at least one SAE broken down by seriousness criteria (fatal, life-threatening, requires hospitalization, results in disability/incapacity, congenital anomaly/birth defect).

SAEs will also be listed in separate listings by product.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.12.1	Summary of Serious Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.12.2	Summary of Serious Adverse Events by System Organ Class and Preferred Term – Full Safety Population
LISTINGS	
15.3.6.1.2	Listing of Serious Adverse Events

12.6.4.2.3 Adverse Events Leading to Discontinuation

Summaries will be presented for AEs leading to withdrawal, by product as described in [Section 12.6.4.2 “Adverse Events”](#).

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.13.1	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.13.2	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Full Safety Population



TFL number	Title
15.2.6.14.1	Summary of Adverse Events Leading to Study Discontinuation by Product Use Category, System Organ Class and Preferred Term – Safety Population
15.2.6.14.2	Summary of Adverse Events Leading to Study Discontinuation by Product Use Category, System Organ Class and Preferred Term – Full Safety Population
LISTINGS	
15.3.6.1.3	Listing of Adverse Events Leading to Study Discontinuation

12.6.4.2.4 Laboratory Abnormalities

The shift in toxicity grades from Baseline to worst grade recorded while in the Randomized period will be presented in tables for the clinical chemistry, hematology and urinalysis parameters. Details related to the toxicity grading of laboratory abnormalities are available in [Section 12.6.4.3 “Clinical laboratory Evaluation”](#).

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.16.1	Summary of Clinical Chemistry Parameters – Safety Population
15.2.6.16.2	Summary of Clinical Chemistry Parameters – Full Safety Population
15.2.6.17.1	Summary of Hematology Parameters – Safety Population
15.2.6.17.2	Summary of Hematology Parameters – Full Safety Population
15.2.6.18.1	Summary of Urinalysis Parameters – Safety Population
15.2.6.18.2	Summary of Urinalysis Parameters – Full Safety Population

12.6.4.2.5 THS 2.2 Device Events

All events relating to the device type will be listed for each subject, including event description, device type the event relates to, severity of event, AE relationship, proposed solution and onset/stop dates/times. Device events will be classified according to PMI device controlled terminology.

A summary table of device events will be presented by product, including:

- Number of device events and the number and percentage of subjects reporting at least one device event.
- Number of device events and the number and percentage of subjects categorized by severity of device event (minor, major)
- Number of device events and the number and percentage of subjects categorized by AE relationship (related, not related)
- Number of device events and the number and percentage of subjects categorized by event description.



Device events and inventory will be listed by product.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.15.1	Summary of THS 2.2 Menthol Device Events – Safety Population
15.2.6.15.2	Summary of THS 2.2 Menthol Device Events – Full Safety Population
LISTINGS	
15.3.6.2	Listing of THS 2.2 Menthol Device Events and Malfunctions

12.6.4.3 Clinical Laboratory Evaluation

Table 22 below lists the hematology, clinical chemistry and urine analysis parameters to be assessed in this study.

Table 22: List of Laboratory Safety Parameters

Hematology	Clinical chemistry	Urine analysis
Hematocrit	A bumin	pH
Hemoglobin	Total protein	Bilirubin
Mean corpuscular hemoglobin	A kaline phosphatase	Glucose
Mean corpuscular hemoglobin concentration	Alanine aminotransferase	Nitrite
Mean corpuscular volume	Aspartate aminotransferase	Red blood cell traces
Platelet count	Blood urea nitrogen	Protein
Red blood cell count	Creatinine	Specific gravity
WBC count	Gamma-glutamyltransferase	
Differential WBC count:	Fasting glucose	
• Neutrophils	Lactate dehydrogenase	
• Basophils	Potassium	
• Eosinophils	Sodium	
• Lymphocytes	Total bilirubin	
• Monocytes	Direct bilirubin	
	Total cholesterol	
	Triglycerides	

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the principal investigator (PI) and assessed for clinical relevance. If the PI considers the abnormal result to be of clinical relevance, then it must be recorded as a concomitant disease at Screening, or if not present at Screening, as an AE during the study. If the condition worsens from screening to after product-use it will be recorded as an AE.

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



Laboratory data will be summarized and listed at Screening and Day 0 for the Pre-Randomization period; and at Baseline, Day of Discharge (Day 6), Day 30 Visit, Day 60 Visit and Day 90 Visit for the Randomized period data together with changes from Baseline. The number and percentage of subjects with normal results, high/low results and abnormal clinical significant result (as defined by PI comment), and CTCAE toxicity grading will be tabulated for laboratory parameters, together with shift in normality (Normal, Abnormal NCS, Abnormal CS) and in CTCAE toxicity grading from Baseline.

Listings for the clinical laboratory data will include the following information: change from Baseline, normal/ high/low (with respect to the reference range), abnormal clinically significant (as defined by the PI comments) and shift from Baseline, the PI comments, the CTCAE grade and the shift in CTCAE grade. Only CTCAE grades greater than zero will be presented.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.16.1	Summary of Clinical Chemistry Parameters – Safety Population
15.2.6.16.2	Summary of Clinical Chemistry Parameters – Full Safety Population
15.2.6.17.1	Summary of Hematology Parameters – Safety Population
15.2.6.17.2	Summary of Hematology Parameters – Full Safety Population
15.2.6.18.1	Summary of Urinalysis Parameters – Safety Population
15.2.6.18.2	Summary of Urinalysis Parameters – Full Safety Population
LISTINGS	
15.3.6.4	Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades
15.3.6.5	Listing of Hematology Data Shift, Changes from Baseline and CTCAE grades
15.3.6.6	Listing of Urinalysis Data Shift, Changes from Baseline and CTCAE grades

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

12.6.4.4.1 Prior and Concomitant Medication

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

All medications will be listed by product using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization-Drug Dictionary Enhanced



[WHO-DDE] Q1 2012). A flag will be presented on the listing indicating whether the medication is prior or concomitant. Prior and concomitant medications will be listed by randomization arm. Prior and Concomitant medications will be summarized by randomization arm for the Safety population showing the number and percent of subjects who used the medication at least once by ATC 1st and 2nd levels and preferred drug name.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.19.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.19.2	Summary of Prior Medication by Preferred Drug Name – Safety Population
15.2.6.20.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.20.2	Summary of Concomitant Medication by Preferred Drug Name – Safety Population
LISTINGS	
15.3.6.3	Listing of Prior and Concomitant Medication

12.6.4.4.2 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -2), Day of discharge (Day 6), Day 30 Visit, Day 60 Visit and Day 90 Visit will be listed by product. Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. The number of subjects and percent with normal, abnormal and abnormal clinically significant results will be tabulated by body systems for the Randomized period at Baseline, day of discharge, Day 30 Visit, Day 60 Visit, and Day 90 Visit, including shifts in normality from Baseline.

Body weight and waist circumference recorded at Admission (Day -2), Day of discharge from Confinement (Day 6), Day 30 Visit, Day 60 Visit and Day 90 Visit; and body height recorded at the Screening visit will also be listed together with BMI. Descriptive statistics of body weight, waist circumference, body height and BMI (BMI will also be categorized as shown in [Section 7.5 "Categorical Variables"](#)), at Baseline and Day of discharge and Day 90 Visit will be presented for the Safety population.

Summaries will be presented for the Safety population by study arm

The data will be presented in the below outputs:



TFL number	Title
TABLES	
15.2.6.24	Summary of Physical Examination of Body Systems– Safety Population
15.2.6.25	Summary of Weight , Waist Circumference and BMI Results – Safety Population
LISTINGS	
15.3.6.10	Listing of Physical Examination Findings, Shift and Changes from Baseline

12.6.4.4.3 Vital Signs

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

Descriptive statistics will be presented for supine systolic and supine diastolic blood pressure, pulse rate and respiratory rate at Baseline, and on every subsequent day of both the confinement and ambulatory periods by product for each study day. Vital signs data will be summarized together with changes from Baseline.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.21	Summary of Supine Vital Signs – Safety Population
LISTINGS	
15.3.6.7	Listing of Vital Signs Data and Changes from Baseline

12.6.4.4.4 Spirometry

Spirometry parameters assessed during the study include:

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

The above data are collected at Screening, Day 0, Day of Discharge (Day 6), and Day 90 Visit. At Screening, data are collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator. All other spirometry assessments are performed without bronchodilator.



Spirometry predicted values will be standardized to the predicted set from the Japanese Respiratory Society. Spirometry data values and normality evaluation will be listed by sequence and study day. Assessments performed after Baseline will be listed together with change from Baseline and shift in normality. Spirometry data from subjects who had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for FEV₁(L), FEV₁ (% pred), FVC(L), FVC(% pred), and FEV₁/FVC at Baseline (pre or without bronchodilator), Day of Discharge (Day 6), and Day 90 Visit by study arm, and overall for the Safety population in the Randomized period. Spirometry data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal non clinically significant/abnormal clinically significant results. Data with and without bronchodilator at Screening will be summarized together with the spirometry data at Day 0 for the Safety population in the Pre-randomization period.

The data will be presented in the below outputs:

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

12.6.4.4.5 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces, i.e. not centrally read. These data include the PR, QT, and QTcB intervals; QRS duration; and heart rate; and normality evaluation (normal, abnormal non-clinically significant, clinically significant, together with any PMI comments to the abnormality). In addition the QTcF value will be presented.

ECG data values and normality evaluations will be listed by product and study day (Screening, Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit) together with changes from baseline and shift in normality. ECG data from subjects which had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for ECG data at Baseline, and Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit by study arm. ECG data will be summarized together with changes from Baseline, and the number and percentage of subjects with normal/abnormal non clinically significant/abnormal clinically significant results.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.22	Summary of ECG Results – Safety Population



TFL number	Title
LISTINGS	
15.3.6.9	Listing of ECG Data and Changes from Baseline

12.6.4.4.6 Assessment of Cough

Cough questionnaire is assessed on a daily basis from Day 0 to Day 6 and Day 30 Visit, Day 60 Visit and Day 90 Visit. Questionnaire details are reported in [Section 7.3.7 "Cough Assessment"](#).

The number and percentage of subjects reporting a cough will be summarized by randomization arm and presented for the day prior to the assessment. The responses to the individual items, including the VAS evaluating the level of cough bother and 3 Likert scales measuring the intensity, the frequency of cough and the amount of sputum production will be listed and summarized on each day by randomization arm, for all subjects who filled in the questionnaire. The answers to the open question related to any other important observation will be listed.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.26	Summary of Cough Assessments Over Study – Safety Population
15.2.6.26.1	Summary of Cough Assessments by Study Day – Safety Population
LISTINGS	
15.3.6.15	Listing of Cough Assessment Results

13 ANALYSIS AND REPORTING**13.1 Interim Analysis and Data Monitoring**

No interim analysis is planned on this study.

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

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

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

13.2 Safety Reporting

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



TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – PP Set
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – PP Set
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set
15.2.5.3.1	Summary of Maximum and Average Number of Products Used per Day - Safety Population
15.2.5.3.2	Summary of Maximum and Average Number of Products Used per Day - Full Safety Population
15.2.6.1.1	Summary of Adverse Events– Safety Population
15.2.6.1.2	Summary of Adverse Events– Full Safety Population
15.2.6.2.1	Summary of Adverse Events by Product Use Category in Ambulatory – Safety Population
15.2.6.2.2	Summary of Adverse Events by Product Use Category in Ambulatory – Full Safety Population
15.2.6.3.1	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.3.2	Summary of Adverse Events by System Organ Class and Preferred Term – Full Safety Population
15.2.6.4.1	Summary of Adverse Events by Product Use Category, System Organ Class and Preferred Term – Safety Population
15.2.6.4.2	Summary of Adverse Events by Product Use Category, System Organ Class and Preferred Term – Full Safety Population
15.2.6.5.1	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.5.2	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Full Safety Population
15.2.6.6.1	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.6.2	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Full Safety Population
15.2.6.7.1	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population



TFL number	Title
15.2.6.7.2	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Full Safety Population
15.2.6.8.1	Summary of Adverse Events Leading to Study Discontinuation by Actual Exposure, System Organ Class and Preferred Term – Safety Population
15.2.6.8.2	Summary of Adverse Events Leading to Study Discontinuation by Actual Exposure, System Organ Class and Preferred Term – Full Safety Population
15.2.6.9.1	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population
15.2.6.9.2	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Full Safety Population
15.2.6.10.1	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.10.2	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Full Safety Population
15.2.6.11.1	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.11.2	Summary of Adverse Events by Product Use Category, System Organ Class, Preferred Term and Severity – Full Safety Population
15.2.6.12.1	Summary of Serious Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.12.2	Summary of Serious Adverse Events by System Organ Class and Preferred Term – Full Safety Population
15.2.6.15.1	Summary of THS 2.2 Menthol Device Events – Safety Population
15.2.6.15.2	Summary of THS 2.2 Menthol Device Events – Full Safety Population

13.3 Topline Results

Topline results, composed of key statistics and study results listings, will be made available to PMI management following database lock and prior to completion of the complete set of TFLs. The topline TFLs are listed in the table below.

TFL number	Title
FIGURES	
15.1.1.1	Forest Plots of Statistical Analysis of Biomarkers of Exposure for Primary Objective – PP Set
15.1.1.2	Biomarker of Exposure for Primary Objective Profile Mean and 95% CI – PP Set



TFL number	Title
TABLES	
15.2.3.1.1	Analysis of COHb, MHBMA, 3-HPMA, S-PMA, Total NNAL versus mCC on Day 5/90 Visit for THS 2.2 Menthol vs mCC for the Primary Objective – PP Set
15.2.4.1.1	Descriptive Statistics of Blood COHb (%) – PP Set
15.2.4.2.1	Descriptive Statistics of MHBMA in 24-hour Urine Collection – PP Set
15.2.4.3.1	Descriptive Statistics of 3-HPMA in 24-hour Urine Collection – PP Set
15.2.4.4.1	Descriptive Statistics of S-PMA in 24-hour Urine Collection – PP Set
15.2.4.5.1	Descriptive Statistics of Total NNAL in 24-hour Urine Collection – PP Set
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – PP Set
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – PP Set
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – PP Set

13.4 Final Analyses

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

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

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

13.5 Clinical Trials.gov Reporting

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



TFL number	Title
TABLES	
15.2.3.1.1	Analysis of COHb, MHBMA, 3-HPMA, S-PMA, Total NNAL versus mCC on Day 5/90 Visit for THS 2.2 Menthol vs mCC for the Primary Objective – PP Set
15.2.1.1	Summary of Subject Disposition – All Screened Subjects

14 DATA PRESENTATION

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

15 REFERENCES

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**16 APPENDICES****16.1 Study Assessments**

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

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up ^v
											Day 30 Visit ± 3 days	Day 60 Visit ± 3 days	Day 90 Visit ± 3 days				
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6	30	31	60	61	90	91	91 to 119
Informed consent for study participation and two informed consents for bio-bankings	•																
Admission/Discharge		•								•						•	
Advice on the risk of smoking and debriefing	•	•								•	•		•			•	
Monitoring/Intensive support for SA arm					•	•	•	•	•	•	•	•	•	•	•		
Inclusion/exclusion criteria	•	•															
Enrolment		•															
Randomization				•													
Demographics, medical history	•																
Concomitant diseases	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Socio-economic questionnaire								•									
Vital signs ^a	•	•	•	•	•	•	•	•	•	•	•		•			•	



	Screening	Confinement Period									Ambulatory Period						Safety Follow-up ^r
											Day 30 Visit ± 3 days	Day 30 Visit ± 3 days	Day 60 Visit ± 3 days	Day 60 Visit ± 3 days	Day 90 Visit ± 3 days	Day 90 Visit ± 3 days	
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6	30	31	60	61	90	91	91 to 119
THS 2.2 Menthol demonstration	•																
THS 2.2 Menthol product test ^s		•															
Collection of mCC butts for accountability			•	•	•	•	•	•	•	•							
Collection tobacco plugs of used Menthol Tobacco Sticks for further analysis					•	•	•	•	•	•	•		•		•		
Collection filters of used Menthol Tobacco Sticks for further analysis					•	•	•	•	•	•							
Collection filters of used Menthol Tobacco Sticks for accountability					•	•	•	•	•	•							
Collection of empty/partially used Menthol Tobacco Stick packs											•		•		•		
CO breath test ^a		•	•	•	•	•	•	•	•	•	•		•		•		
B: BoExp in blood: COHb _i			•	•	•	•	•	•	•	•	•		•		•		
B: BoExp to nicotine in plasma: nicotine, cotinine ^j				•	•	•	•	•	•	•	•		•		•		



	Screening	Confinement Period									Ambulatory Period						Safety Follow-up ^y
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6	30	31	60	61	90	91	91 to 119
MCEQ (modified version; THS 2.2 Menthol and mCC arms) ^z			•	•	•	•	•	•	•		•		•		•		
HST (THS 2.2 Menthol and mCC arms) ⁴				•	•			•			•		•		•		
HST questionnaire				•				•			•		•		•		
Assessment of cough ¹				•	•	•	•	•	•	•		•		•		•	
Preference product question		•															
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
U: Bio-banking for BoExp and risk markers (see Table A2) ^a				•					•						•		
B: Bio-banking for BoExp and risk markers ^a				•						•						•	
B: Bio-banking for transcriptomics ^a				•						•						•	

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandin F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; B = blood sample required; BMI = body mass index; BoExp = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; FTND = Fagerström Test for Nicotine Dependence; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; HST = human smoking topography; HIV = human immunodeficiency virus; hs-CRP = high-sensitive C-reactive protein; LDL = low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule; THS = tobacco heating system; U = urine sample required; WBC = white blood cell count; TC = total cholesterol; TG = triglycerides.

^a Systolic and diastolic blood pressure, pulse rate, and respiratory rate (systolic and diastolic blood pressure will also be evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 91)).



- b Including height (only at Screening), body weight and calculated BMI. Weight will be evaluated also as risk marker on Day 0 and Day 90 Visit (Day91)
- c Waist circumference will be evaluated also as risk markers on Day -2 and Day 90 Visit (Day 91).
- d At screening, spirometry without bronchodilator will be done first, and then, spirometry with bronchodilator. At screening, spirometry has to be conducted at least 1 hour after smoking. Furthermore, spirometry without bronchodilator will be performed prior to product use at Day 0 (baseline values), on Day 6, and Day 90 Visit (on Day 91 for comparison with the baseline values).
- e WBC, platelet count, from the safety laboratory panel to be evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61) and Day 90 Visit (Day 91). Blood glucose, TG, and TC from the safety laboratory panel to be evaluated also as risk markers on Day 0, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91).
- f Pre-study chest X-ray (with anterior-posterior and left lateral views) may be used, if performed within 6 months prior to Screening.
- g THS 2.2 Menthol product test to be conducted as the last procedure of eligibility check at Day -2 (and after urine pregnancy test has been confirmed negative in female subjects to exclude pregnancy).
- h CO breath test; Days -1 to Day 5 the test will be conducted four times per day. The first test should be conducted within 15 minutes prior to the first product use (for subjects in the Menthol 2.2 and mCC arms) and between 08 00 AM-09 30 AM for subjects in the SA arm. The other three tests should be conducted as described in section 9 of the protocol. Day -2, Day 6, Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90) once during the visit, irrespective of the time of product use.
- i COHb; Assessments should be done in conjunction with CO breath tests, where applicable. Day -1 to Day 4 one blood sample in the evening between 08 00 PM-09 30 PM.
- Day 5 one blood sample within 15 minutes prior to product use (for subjects in THS 2.2 Menthol and mCC arms) and between 08 00 AM-09 30 AM for subjects in the SA arm. The three other blood sampling will be conducted as described in section 9 of the protocol.
- Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90) one blood sample to be collected during the visit, irrespective of the time of product use.
- j Nicotine/cotinine; Day 0 to Day 4 (all study arms) one blood sample between 08 00 PM-09 30 PM.
- Day 5 and Day 6 (THS 2.2 Menthol and mCC arms) one sample within 15 minutes prior to the product use; eight blood samples after product use (T0), each at 2 hour intervals. On Day 6, two blood samples will be drawn. The first sample will be 20 hours after T0 and the second blood sample will be 24 hours after T0 (with T0 being the time of the first product use on Day 5).
- Day 5 and Day 6 (SA arm) on Day 5, one blood sample in the evening between 08 00 PM-09 30 on Day 5 and one blood sampling between 08 00 AM-09 30 AM on Day 6.
- Day 30 Visit (Day 30), Day 60 Visit (Day 60), Day 90 Visit (Day 90) (all study arms) one blood sample to be drawn during the visit, irrespective of the time of product use.
- k To be evaluated also as risk markers on Day 0, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91).
- l To be evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91).
- m To be evaluated also as risk markers on Day 0, and Day 90 Visit (Day 91).
- n To be evaluated also as risk markers on Day 0, Day 3, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90).
- o Daily during ambulatory period only (from time of Discharge on Day 6 to Day 90 only). Use of any tobacco/nicotine containing products will be captured in the e-diary.
- p QSU-brief Daily, from Day -1 to Day 5 and at every visit during the ambulatory period, i.e. Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90).
- q MNWS daily from Day 0 to Day 6 prior product use but no later than 10 00 AM and at every visit during the ambulatory period no later than 10 00 AM, i.e. Day 30 Visit (Day 31), and Day 60 Visit (Day 61) irrespective of time of product use and on Day 90 Visit (Day 91) prior to smoking.
- r MCEQ Day -1 to Day 5 on a daily basis, and on Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90). On Day -1 and Day 0, MCEQ will be asked to all subjects. From Day 1, MCEQ will be asked to THS 2.2 Menthol and mCC arms only.
- s On Day 0, HST assessment will be done in all subjects smoking mCC compatible with the HST SODIM® device. On Day 1, Day 4, Day 30 Visit (Day 30) and Day 60 Visit (Day 60) and Day 90 Visit (Day 90), HST. Smoking topography with the HST device will not be done in subjects smoking mCC that are incompatible with the HST SODIM® device (e.g. slim mCC). No HST assessments will be done in subjects in the SA arm.



tough questionnaire to be done daily from Day 0 to Day 6 prior product use but no later than 10:00 AM and at every visit during the ambulatory period no later than 10:00 AM, i.e. Day 30 Visit (Day 31), and Day 60 Visit (Day 61) irrespective of time of product use and Day 90 Visit (Day 91) prior to smoking.

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

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

Table A2 Schedule for 24-hour Urine Collection Assessments

	Baseline Period 24- hour urine	Confinement Exposure Period 24-hour urine					Ambulatory Exposure Period 24-hour-urine		
	Day 0 to Day 1	Day 1 to Day 2	Day 2 to Day 3	Day 3 to Day 4	Day 4 to Day 5	Day 5 to Day 6	Day 30 to Day 31	Day 60 to Day 61	Day 90 to Day 91
BoExp in urine ^a	•	•	•	•	•	•	•	•	•
Creatinine	•	•	•	•	•	•	•	•	•
11-DTX-B2, 8-epi- PGF2 α	•					•	•	•	•
Ames test	•					•			•
Bio-banking ^b	•					•			•

^a MHBMA, 3-HPMA, S-PMA, Total NNAL, 1-OHP, total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ.

^b Samples will only be taken if additional consent for the relevant sample bio-banking is given by the subject

Abbreviations: 1-NA = 1-aminonaphthalene; 2-NA = 2-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; 8-epi-PGF2 α = 8-epi-prostaglandin F2 α ; 11-DTX-B2 = 11-dehydro-thromboxane B2; BoExp = biomarker(s) of exposure; CEMA = 2-cyanoethylmercapturic acid; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropyl-mercapturic acid; NEQ = nicotine equivalents; Total NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; total NNN = N-nitrosornicotine; MHBMA = monohydroxybutenyl mercapturic acid; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid.



16.1.8.2 Statistical Posthoc Analysis Plan - Spirometry



Wakenshaw, Louise

From: Baker, Gizelle
Sent: 12 May 2015 08:55
To: Luedicke, Frank; Lama, Nicola
Cc: de La Bourdonnaye, Guillaume; Haziza, Christelle; Donelli, Andrea (contracted)
Subject: RE: Post-hoc analysis plan

Dear Nicola

Please accept this as my approval to move forward with this Post-Hoc Analysis.

Kind regards,
Gizelle

From: Luedicke, Frank
Sent: May-12-2015 8:53 AM
To: Lama, Nicola; Baker, Gizelle
Cc: de La Bourdonnaye, Guillaume; Haziza, Christelle; Donelli, Andrea (contracted)
Subject: RE: Post-hoc analysis plan

Please go ahead with the Post-hoc analysis.
Also, I would like to obtain FEV1 REXA 07 JP by EOB Today.
Thanks in advance, Frank

From: Lama, Nicola
Sent: mardi 12 mai 2015 07:55
To: Luedicke, Frank; Baker, Gizelle
Cc: de La Bourdonnaye, Guillaume; Haziza, Christelle; Donelli, Andrea (contracted)
Subject: Post-hoc analysis plan

Dear All,

Please find below the post-hoc analysis plan we discussed.



Thanks in advance for letting us have your approval.

We want to highlight that the results we are producing at the current stage are only preliminary because the PP sets are not yet final.

Kind regards,

Nicola

Post-hoc Analysis Plan for Spirometry data

Version:1.0

Date: 12-May-2015

Studies:

- ZRHM-REXA-07-JP and ZRHM-REXA-08-US

Objective:

- To assess the respiratory clinical risk endpoint in ambulatory setting in smokers switching from mCC to THS 2 2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoint

- Forced expiratory volume in 1 second (FEV1) [% pred] at Day 90 Visit.

Reason for the Analysis

- The effect of THS 2.2 on this endpoint "FEV1 [%pred]" is of interest because one of the primary endpoints in ERS study. Therefore these results may aid in the design and planning of the ERS, ERS Extension and Post-Market Cohort Studies. Also these data may be useful for scientific and regulatory engagement purposes.

Limitation of Analysis/ Interpretation of Analysis

For interpretation purposes, however, it is acknowledged that this endpoint is planned to be assessed:

- o After 6-months of exposure in ERS study as compared to the 3-month endpoint in the REXA studies
- o Post-bronchodilator FEV1 assessment is one of the primary endpoint in ERS study as compared with the assessment in the REXA studies where the spirometry is performed without a bronchodilator.

Analysis population, subgroup/stratification factors

- PP set at Period 4, as defined in SAP
- Currently no subgroup analysis on these data are planned

Planned Analysis

- Endpoint will be analyzed as a difference between the two exposure groups
- The same analysis model adopted for the QC of the risk markers at Day90 (table 15.2.4.25.1 "Analysis of Risk Markers - PP Set") will be used to produce the results of this post-hoc analysis.
- The analysis will be reported in a tabular format similar to the shell of table 15.2.4.25.1.



- Successful QC results for the risk markers in table 15.2.4.25.1 from the main study will be considered sufficient for validation purposes of the code implemented in this post-hoc analysis. In case such QC is not successful, results will be provided with a remark highlighting their draft nature and their limited validation until the results are passed QC.

Timeline

- Results will be produced according with timelines of the PMI review comments for the top line results.

NOTICE: This e-mail may contain confidential information, which should not be copied or distributed without authorization. If you have received this e-mail message by mistake, please inform the sender and delete it from your system. Please note that, for the efficient preservation of Company records that may be required for litigation, e-mail messages sent to the author of this message will be copied and may be retained in a secure repository.

NOTICE: This e-mail may contain confidential information, which should not be copied or distributed without authorization. If you have received this e-mail message by mistake, please inform the sender and delete it from your system. Please note that, for the efficient preservation of Company records that may be required for litigation, e-mail messages sent to the author of this message will be copied and may be retained in a secure repository.

NOTICE: This e-mail may contain confidential information, which should not be copied or distributed without authorization. If you have received this e-mail message by mistake, please inform the sender and delete it from your system. Please note that, for the efficient preservation of Company records that may be required for litigation, e-mail messages sent to the author of this message will be copied and may be retained in a secure repository.



16.1.8.3 Statistical Posthoc Analysis Plan - HST (PH02)



STATISTICAL POSTHOC ANALYSIS PLAN

A randomized, controlled, open-label, 3-arm parallel group, multi center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting

Study Product: Tobacco Heating System 2.2 Menthol

Study Reference No.: ZRHM-REXA-07-JP

Post-hoc Analysis Reference No: ZRHM-REXA-07-JP_PH02

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

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

**1 STATISTICAL POSTHOC ANALYSIS PLAN APPROVAL****SIGNATURES**

By signing this page the posthoc Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this posthoc analysis.

Nicola Lama, PhD
Senior Scientist/ Biostatistics
Study Biostatistician
Philip Morris Product S.A.

09 DEC 2015

Date

Gizelle Baker, PhD
Director Epidemiology and Biostatistics
Philip Morris Product S.A.

14 DEC 2015

Date

Andrea Donelli
Study Scientist
Philip Morris Product S.A.

14.12.2015

Date

Anthony Bruchet
Associate Scientist - HST
Philip Morris Product S.A.

09 DEC 2015

Date



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3 INTRODUCTION

This posthoc SAP has been developed to supplement the statistical analysis described in the SAP of the ZRHM-REXA-07-JP study (final version 2.0 dated 07 Nov 2014) after the study database lock on 12 Nov 2014.

This posthoc SAP describes the methodology and statistical considerations for the posthoc analyses aimed at supporting the results of the Human Smoking Topography (HST) endpoints measured in the ZRHM-REXA-07-JP study. The results of this additional analysis will increase the interpretability of HST data by facilitating the comparison with the results obtained in previous studies conducted on the same study product, in particular ZRHR-REXC-03-EU and ZRHR-REXC-04-JP studies

4 VERSION HISTORY

Version	Date of Revision	Revision
1.0	09 Dec 2015	Final



5 ANALYSIS OBJECTIVES AND ENDPOINTS

The objective and endpoints of this posthoc analysis are:

1. To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing smoking mCC:

Endpoints (Day 1, Day 4, Day 30, Day 60, and Day 90):

- The following parameters measured from the HST device.

– Total number of puffs.	– Total smoking duration.
– Total puff volume.	– Total work.
– Average puff volume.	– Average work.
– Average puff duration.	– Average pressure drop.
– Total puff duration.	– Average peak pressure drop.
– Average flow.	– Smoking intensity.
– Average Peak flow.	– Puffing time index.
– Total inter puff interval.	– Puff frequency.
– Average inter puff interval.	

6 DERIVED AND COMPUTED VARIABLES

No new variable will be derived in this posthoc analysis. All derived and computed variables are included in the study ADaM datasets (final version date 07-Jul-2015), generated as per the study SAP.

7 ANALYSIS POPULATIONS

All figures, summaries and analyses will be performed on the Per Protocol (PP) Set.

In accordance with the study SAP, the PP Set is defined as the subset of all randomized subjects who have no major protocol deviations impacting evaluability as defined in the study SAP. The PP Set is assessed for each product use time period, considering the product deviations occurring only that period, independent of any exclusion from the population in previous periods. The analysis study periods are defined as follows:



- Period 1 ([Day 1-Day 6 confinement])
- Period 2 ([Day 6 ambulatory-Day 30 Visit])
- Period 3 ([Day 30 Visit-Day 60 Visit])
- Period 4 ([Day 60 Visit-Day 90 Visit])

The analysis population flag variables produced in the study ADaM datasets will be used for the analysis.

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

The general considerations detailed within Section 12.1 of the study SAP are applicable to this posthoc SAP.

This analysis will be performed to support the results generated in the SAP and facilitate cross study interpretation, therefore no adjustment will be made for multiple comparisons.

8.2 Planned Statistical Analyses

8.2.1 Human Smoking Topography Parameters

The daily average HST parameters derived in the main study will be summarized with geometric means and 95% CI along with their percent changes from baseline (table 15.2.4.42.1). In addition the geometric means and 95% CI will be presented graphically by randomization arm (figure 15.1.2.10.1).

The statistical analysis of the daily averaged per-cigarette HST parameters will be performed on Days 1, 4, 30, 60 and 90 separately using an ANCOVA model with terms for baseline score, sex, average daily mCC consumption over the last 4 weeks as reported during screening, and randomization arm. The following SAS code will be used for the analysis:

```
Proc mixed data=_data_;  
  
Class randomization_arm sex cigarette_cons;  
Model log_HST_par = log_baseline sex cigarette_cons randomization_arm;  
Lsmean randomization_arm / pdiff =control('mCC') alpha=0.05 cl;  
Run;
```



HST parameters will be analyzed on the log scale, and the least squares (LS) means and estimate of the difference and the 95% CI will be back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), and two-sided 95% CI will be presented tabulated (table 15.2.4.43.1).

9 TIMELINES FOR ANALYSIS

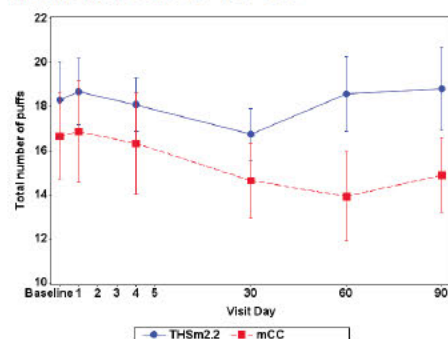
Results will be produced after the finalization of the clinical study report (CSR).

10 DATA PRESENTATION

Results will be produced after the finalization of the clinical study report (CSR). Results will be reported in an addendum to the CSR.

Results will be produced as per the following templates and with the same general rules provided in the study Table Listings and Figures Template (Final v1.0, dated 07Nov2014). Final results will be reported in an addendum of the final CSR.

Figure 15.1.2.10.1 HST Parameters Averaged Over the Visit Geometric Mean and 95% CI - PP Set



Note: mCC = Conventional menthol cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: Baseline is the last assessment prior to first product use in CC/THS 2.2 arms on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1.

Programmers' note: Repeat for all HST parameters (averaged over the visit) as in 15.2.4.43.1



Table 15.2.4.43.1 Analysis of HST Parameters per Cigarette - PP Set

Parameter: Total number of puffs (average over visit)

Time Point	Statistic	THSm2.2	mCC	THSm2.2 : mCC ratio
Day 1	n	XX	XX	
	Geometric LS Mean (CV%)	XX.XX	XX.XX	XX.XX (XX.XX)
	95% CI	XX.XX, XX.XX	XX.XX, XX.XX	XX.XX, XX.XX

Note: mCC = Menthol conventional cigarettes; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: Adjusted geometric least squares (LS) means and confidence intervals (CIs) from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at screening as fixed effect factors.

Programmers' note: continue with timepoints Day 4, 30, 60, and 90. Repeat for all HST parameters (averaged over the visit): Total Puff Volume (mL), Average Puff Volume (mL), Average Puff Duration (s), Total Puff Duration (s), Average Flow (mL/s), Peak Flow (mL/s), Total Inter Puff Interval (mL/s), Average Inter Puff Interval (s), Total Smoking Duration (s), Total Work (mJ), Average Work (mJ), Average Pressure Drop (mmWg), Average Peak Pressure Drop (mmWg), Smoking Intensity (mL/s), Puffing Time Index (%) and Puff Frequency (puffs/min)



Table 15.2.4.42.1 Descriptive Statistics of HST Parameters - PP Set

Parameter: Total number of puffs (average over visit)

Product Use Time Period: Period 1

Time Point	Statistic	THSm2.2 (N=xx)		mCC (N=xx)		SA (N=xx)	
		Raw value	% Change(*)	Raw value	% Change(*)	Raw value	% Change(*)
Baseline	N	xx		xx		xx	
	Missing, n(%)	xx (xx.x)		xx (xx.x)		xx (xx.x)	
	Geometric Mean (CV)	xx (xx.xx)		xx (xx.xx)		xx (xx.xx)	
	95% CI	xx.xx, xx.xx		xx.xx, xx.xx		xx.xx, xx.xx	
	Median	xx.xx		xx.xx		xx.xx	
	Q25, Q75	xx.xx, xx.xx		xx.xx, xx.xx		xx.xx, xx.xx	
	Min, Max	xx.x, xx.x		xx.x, xx.x		xx.x, xx.x	

Note: mCC = Menthol conventional cigarettes; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: Percentages are based on the number of subjects indicated in the column header (N).

Note: * % change from baseline where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Programmers' note: continue with timepoints Day 1, 4, 30, 60, and 90 within each study period, including %change data. Repeat Baseline row as first row within each study period since this will be different depending on the number of subjects in the PP Set in each period. Repeat for all HST parameters (averaged over the visit) as in 15.2.4.43.1.