STATISTICAL ANALYSIS PLAN

A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching from conventional cigarettes to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to smokers continuing to use conventional cigarettes, for 5 days in confinement

Study Product: Tobacco Heating System 2.2

Sponsor Reference No.: ZRHR-REXC-04-JP
CDARO No.: 1001000-8278004

Sponsor:
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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

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

[redacted]

Sponsor approval:

[redacted]

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3 INTRODUCTION

This SAP has been developed to supplement the statistical analysis described in the clinical study protocol (final 2.0 dated 08 July 2013).

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 3.0 (dated 29 October 2013).
- Biostatistical Addendum – Subject Randomization List version 1.0 (08 April 2013).

3.1 Revision History

Version	Date of Revision	Revision
2.0	16 June 2014	• Section 11.1 Major Protocol Deviations: o CO breath test > 10 ppm on Day 1 is not considered as a major protocol deviation for subjects in the SA arm.
1.0	24 February 2014	Original SAP

4 ABBREVIATION OF 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
11-DTX-B2	11-dehydro-thromboxane B2
ADaM	Analysis Data Model
AE/SAE	Adverse Event/ Serious Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic and Chemical
$AUC_{0\text{-}24\ h}$	The area under the curve from 0 to 24 h
AUQ	Above upper limit of quantification
B[a]P	3-hydroxybenzo(a)pyrene
BMI	Body Mass Index
BoExp	Biomarkers of exposure
CAF	Caffeine
C_{avg}	Weighted average concentration of nicotine or cotinine over 24 hours
CC	Conventional Cigarettes
CEMA	2-cyanoethylmercapturic acid
CI	Confidence Interval
[redacted]	[redacted]
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
C_{peak}	Peak nicotine or 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
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
glm	General Linear Model
HEMA	2-hydroxyethyl mercapturic acid
HIV	Human Immunodeficiency Virus
HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
HST	Human Smoking Topography
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
IXRS	Interactive Web Response System
LLOQ	Lower Limit of Quantification
LS	Least Squares
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-nitrosonornicotine
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	Urge-to-Smoke Questionnaire of Smoking Urges Brief
QTcB	QT Interval Corrected using Bazett's Formula
QTcF	QT Interval Corrected using Fridericia's Formula
SA	Smoking Abstinence
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Tabulation Module
SMAR	Smoking article
SOC	System Organ Class
SOP	Standard Operating Procedure
S-BMA	S-benzylmercapturic acid
S-PMA	S-phenylmercapturic acid
THS	Tobacco Heating System
TFL	Tables, Figures, and Listings
t_{peak}	Time to peak concentration
ULOQ	Upper Limit of Quantification
UV	Ultra violet
VAS	Visual Analogue Scale
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.
Conventional cigarette (CC)	The term 'conventional cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
CC incompatible with Human Smoking Topography (HST) device	All CCs that are incompatible with the HST device (e.g., slim CC).
Day of Discharge	Day 6.
Enrollment	On Day -2 for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily met and the subject is willing and ready to use THS 2.2 (the test of THS 2.2 is the last assessment prior to enrollment).
Exposure period	06:30 AM of Day 1 until 11:00 PM of Day 5.
Randomization	Assignment of the subject randomization number in the Interactive Web and Voice Response System (IXRS). This can be done any time on Day 0, however, subjects are not informed of their randomization arm prior to Day 1.
Run-in period	Admission to site until 06:29 AM of Day -1.
Safety follow-up	After the time of Discharge, a 7-day safety follow-up will be done for the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site.
Screening failure	Subjects who are not enrolled will be considered a screening failure and will be replaced by other subjects.
Tobacco Heating System 2.2 (THS 2.2)	THS 2.2 is comprised of the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective and Endpoints

1. To demonstrate the reduction of primary biomarkers of exposure (BoExp) in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   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.

5.2 Secondary Objectives and Endpoints

1. To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   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:
     - Total 1-hydoxypyrene (1-OHP),
     - Total N-nitrosonornicotine (Total 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).
     - Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL).

2. To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:
   - 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.
  - 3-HPMA.
  - S-PMA.
  - 1-OHP.
  - Total NNN.
  - 4-ABP.
  - 1-NA.
  - 2-NA.
  - o-tol.
  - CEMA.
  - HEMA.
  - B[a]P.
  - HMPMA.
  - S-BMA.
  - Total NNAL.

3. To determine the levels of nicotine on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.

   Endpoints:
   - Nicotine equivalents (NEQ) (expressed in quantity excreted and concentration adjusted for creatinine) in 24-hour urine on Day 5 and from Day 1 to Day 5.
   - Plasma nicotine and cotinine concentrations.

4. To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to smoking abstinence (SA).

   Endpoints:
   - COHb in blood (expressed as % saturation of hemoglobin).
   - CO (expressed as ppm) in exhaled breath.
   - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine:
     - MHBMA.
     - 3-HPMA.
     - S-PMA.
     - 1-OHP.
     - Total NNN.
     - 4-ABP.
     - 1-NA.
     - 2-NA.
     - o-tol.
     - CEMA.
     - HEMA.
     - B[a]P.
     - HMPMA.
     - S-BMA.
     - Total NNAL.
     - NEQ.

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

   Endpoints:
   - Peak (highest concentration value along the day) on Day 5 in plasma.

- 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 changes in Cytochrome P450 1A2 (CYP1A2) enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.

   Endpoints:
   - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5.

7. To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:
   - Number of THS Tobacco Sticks and CC used each day for each subject from Day -1 to Day 5.

8. To monitor the safety profile during the study.

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

5.3 Exploratory Objectives and Endpoints

1. To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and smokers switching from CC to SA:

   Endpoints:
   - Ames Mutagenicity test (YG1024+S9).
   - Questionnaire of Smoking Urges (brief version) [QSU-brief] total score, factor 1 (relief) and factor 2 (reward) (**Cox et al. 2001**).
   - Minnesota Nicotine Withdrawal Scale (MNWS) total score (**Hughes and Hatsukami 2008**).

- CYP2A6 enzymatic activity as molar ratio of 3-hydroxycotinine and cotinine
- Selected risk markers (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine:
  - 8-epi-prostaglandine F2α (8-epi-PGF2α)
  - 11-dehydro-thromboxane B2 (11-DTX-B2)

2. To evaluate in smokers switching from CC to THS 2.2, smokers continuing smoking CC and smokers switching from CC to SA the relationship between[1]:

Endpoints:

- Primary and secondary BoExp and NEQ:
- NEQ in urine by:
  - Blood COHb.
  - Exhaled CO

  and urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine
  - MHBMA.
  - 3-HPMA.
  - S-PMA.
  - 1-OHP.
  - Total NNN.
  - 4-ABP.
  - 1-NA.
  - 2-NA.
  - o-tol.
  - CEMA.
  - HEMA.
  - B[a]P.
  - HMPMA.
  - S-BMA.
  - Total NNAL.

[1] *The reporting of this objective will be the subject of a separate report.*

- Selected risk markers and NEQ[2] :
- NEQ in urine by:
  and urinary risk markers (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine
  - 8-epi-PGF2α.
  - 11-DTX-B2.

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

   Endpoints:
   - The subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ) (**Cappelleri et al. 2007**).
   - The following parameters measured per cigarette from the human smoking topography (HST) device.
     - Total number of puffs.
     - Total puff volume.
     - Average puff volume.
     - Average puff duration.
     - Total puff duration.
     - Average flow.
     - Average Peak flow.
     - Total inter puff interval.
     - Average inter puff interval.
     - Total smoking duration.
     - Total work.
     - Average work.
     - Average pressure drop.
     - Average peak pressure drop.
     - Smoking intensity.
     - Puffing time index.
     - Puff frequency.
     - HST questionnaire.

4. To describe the following parameter over the course of the study in smokers switching from CC to THS 2.2:

   Endpoints:
   - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.

5.4 Additional Endpoints

The following additional safety assessments will be made:

- Serology for human immunodeficiency virus (HIV) 1/2 and Hepatitis B and C
- Urine pregnancy test (females only), urine cotinine test, urine drug screen
- Alcohol breath test
- Chest X-ray
- Nicotine dependence to be assessed with the Fagerström Test for Nicotine Dependence (FTND) revised version (**Fagerström et al. 2012**)

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[2] *This objective has changed from the protocol, see Section 9, 'CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS'.*

5.5 Study Hypotheses And Evaluation Criteria

5.5.1 Hypotheses

The hypothesis to be tested for each of the primary and secondary BoExp is that the geometric mean level on Day 5 of the BoExp for THS 2.2 is lower relative to CC.

5.5.2 Evaluation Criteria

The study will be considered successful if the study demonstrates a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb in the THS 2.2 arm compared to the CC arm (as measured on Day 5), 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, single-center study with a stratified randomization by sex (male vs. female) and average daily CC consumption over the last 4 weeks as reported during the Screening Visit (10 - 19 CC/day vs. >19 CC/day). (**Figure 1 Study Flowchart**).

In total, 160 eligible, healthy smoking subjects will be randomized into one of the three study arms in **"Table 1 Definition of Study Arms"**.

Table 1 Definition of Study Arms

Study arm	Number of subjects
THS 2.2	80
CC	40
SA	40

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

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 site staff will demonstrate the use of THS 2.2.

Subjects will be admitted to the clinical site on Day -2 (Admission). At Admission, in female subjects, the urine pregnancy test must be negative before the product test of THS 2.2 is performed. The THS 2.2 product test, (use of up to 3 THS Tobacco Sticks) is the last procedure of the eligibility assessments, prior to enrollment. After the inclusion and exclusion criteria have been satisfactorily met, only subjects willing and able to use THS 2.2 will be enrolled in the study, to minimize the drop-out rate during the course of the study.

Subjects are enrolled on Day -2, and then randomized on Day 0. From Day-2 to Day 0, all subjects will continue smoking their single preferred brand of CC and baseline values will be recorded on Day -1 and Day 0. On Day 0, subjects will be randomized to 1 of the 3 study arms (see **"Table 1 Definition of Study Arms"**). Subjects will be informed of their randomized study arm by the study site staff on Day 1 prior to 06:30 AM.

Although subjects are exposed to CC during the baseline procedures, the study exposure period (from Day 1, 06:30 AM to Day 5, 11:00 PM) will consist of 5 days of *ad libitum* use of the assigned product between 06:30 AM and 11:00 PM each day (THS 2.2 and CC arms). Use of any tobacco/nicotine containing product other than the assigned product will not be allowed and may, at the discretion of the Principal Investigator (PI) or designee, result in the subject's withdrawal from the study.

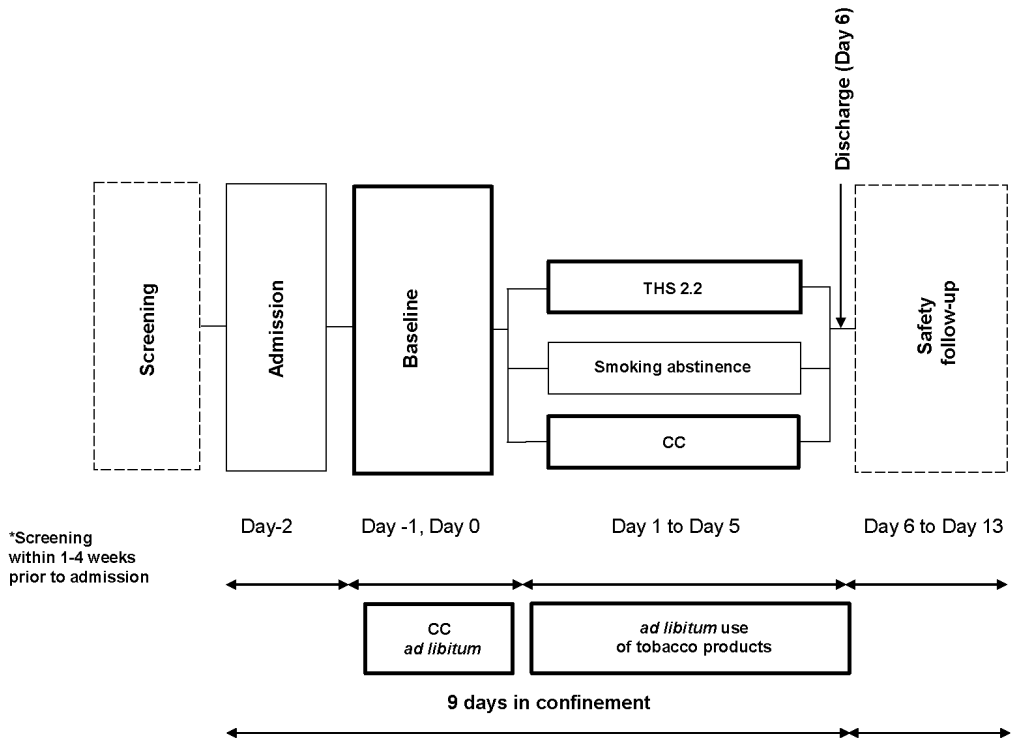
Subjects in the SA arm will be asked to abstain from using any nicotine/tobacco containing product and will not be provided with medication to support SA. Subjects will be provided with psychological support during the period of smoking abstinence.

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

Subjects will be discharged from the investigational site in the morning of Day 6 after all safety examinations of the Day of Discharge have been conducted. Use of CC will be allowed on Day 6, but only after spirometry has been performed.

After Discharge, subjects will enter into a 7-day safety follow-up to capture spontaneously reported new AEs/SAEs and for active follow-up of ongoing AEs/SAEs. Any AE will in general be followed up until resolved, stabilized (i.e., no worsening of the event), or until a plausible explanation for the event has been found. The end of study (EOS) is defined as the end of the 7-day safety follow-up period.

Figure 1 Study Flowchart



Abbreviations: THS 2.2 = Tobacco Heating System 2.2; CC = conventional cigarettes.

6.1.1 Timing of Confinement Period

The 9 day confinement period consists of:

- The Admission Day (Day -2).
- The run-in period, from Admission on Day -2 until 06:29 AM of Day -1.
- The baseline period, from Day -1, 06:30 AM until Day 1, 06:29 AM.
- The exposure period, from Day 1, 06:30 AM until Day 5, 11:00 PM.
- The day of Discharge, Day 6, from Day 5 (11:01 PM) to time of Discharge on Day 6.

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.
5. Subject smokes at least 10 commercially available non-menthol CCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/CC, as labeled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject has been smoking for at least the last three 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 5 days.
8. The subject is ready to accept using the THS 2.2.

6.2.2 Exclusion Criteria

The exclusion criteria are:

1. As per Investigator judgment, the subject cannot participate in the study for any reason.
2. A subject who is legally incompetent, physically or mentally incapable of giving consent.
3. The subject has medical condition requiring smoking cessation, or clinically relevant diseases in the judgment of the Investigator.
4. The subject has a body mass index (BMI) <18.5 or ≥ 32 kg/m^2.
5. As per Investigator judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention which may interfere with the study participation and/or study results.
6. The subject has used nicotine-containing products other than commercially available CC (either tobacco-based products or nicotine-replacement therapy) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
7. The subject has received medication (prescribed 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 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 or subject's safety.
9. Concomitant use of non-steroidal 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 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 surface antigen or hepatitis C virus.
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 Interactive Web and Voice Response System (IXRS).

Subjects will be randomized to 1 of the 3 arms. Each sex and each of the current CC consumption levels (10-19 CC/day and >19 CC/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 CC/day, female smokers who smoke 10-19 CC/day, male smokers who smoke >19 CC/day, and female smokers who smoke >19 CC/day). Block randomization is used within each stratum (i.e., each list) in a 2:1:1 ratio (THS 2.2:CC:SA).

The randomization scheme is generated by a statistical division within [redacted] and none of the study team (including study sponsor and [redacted] 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 in the data review and data analysis process. In particular, PMI and [redacted] 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 [redacted] 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 the [redacted] and PMI study team before database lock, with no access to the randomization information. Full details will be available in the data review plan.

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

Data will not 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

Compliance for all arms will be ensured by strict distribution of the products (product by product) and collection of used THS Tobacco Sticks and the CC butts after use will be documented in appropriate logs.

In addition, in subjects in the SA arm, the compliance will be chemically verified using exhaled CO breath. The cut-off point for the CO breath test value to distinguish subjects in the SA arm with 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.

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 value 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:

$$QTcB = \frac{QT}{\sqrt[2]{\left(60/HR\right)}}$$

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

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

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

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

7.1 Biomarkers

Values below the Lower Limit of Quantification (LLOQ) for BoExp and risk markers will be imputed using LLOQ/2. For values above the Upper Limit of Quantification (ULOQ) i.e., preceded by a ">", for example ">xx", the numerical xx will be used for calculation and reporting in summary tables. The number of values below LLOQ or above ULOQ will be presented in each summary table.

7.1.1 Biomarkers of Exposure

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

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

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

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

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

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

7.1.2 Risk Markers

For those risk markers measured in urine an adjustment of the concentration for creatinine in urine will be calculated as:

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

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

The quantity excreted for the risk markers measured in urine over 24 hours will be calculated as:

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

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

7.1.3 Nicotine Equivalents

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

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

N.B. All concentrations must be in µmol/L before applying the above formula.

The conversion factors will be applied as follows:

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

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

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

7.1.4 CYP1A2

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

The conversion factor will be applied as follows:

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

The 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.

7.1.5 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.

7.1.6 Laboratory Parameters

Values below the Lower LLOQ will be handled as described in Section **7.1**, "**Biomarkers**".

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. 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 ($AUC_{0\text{-}24\ h}$) by 24, where the $AUC_{0\text{-}24\ h}$ 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

All used questionnaires, except the cough and HST questionnaires, are available as a validated questionnaire in Japanese. The cough and HST questionnaires will be forward-translated and back-translated with subsequent independent verification.

7.3.1 Fagerström Test for Nicotine Dependence (FTND)

The FTND will be used in its revised version (**Heatherton et al 1991**), as updated in 2012 (**Fagerström et al. 2012**). These questions are to be answered by the subject themselves. It is conducted at Screening only to determine subject's 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 ▪ 6 to 30 minutes ▪ 31 to 60 minutes ▪ After 60 minutes	3 2 1 0
2	Do you find it difficult to refrain from smoking in places where it is forbidden?	▪ Yes ▪ No	1 0
3	Which cigarette would you hate most to give up?	▪ The first one in the morning ▪ Any other	1 0
4	How many cigarettes per day do you typically smoke?	▪ 10 or less (up to ½ pack) ▪ 11 to 20 (a little more than ½ pack, up to a full pack) ▪ 21 to 30 (a little more than a pack, up to 1½ packs) ▪ 31 or more (more than 1½ packs)	0 1 2 3

Table 3: Scoring for the Fagerstrom Test for Nicotine Dependence

	FTND Question	Response	Score
5	Do you smoke more frequently during the first hours after waking than during the rest of the day?	▪ Yes ▪ No	1 0
6	Do you smoke if you are so ill that you are in bed most of the day?	▪ Yes ▪ No	1 0

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

The QSU-brief (**Cox et al. 2001**) is a self-reported questionnaire completed daily from Day -1 to Day 5 between 08:00 PM and 11:00 PM.

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.

7.3.3 Modified Cigarette Evaluation Questionnaire

The MCEQ (**Cappelleri et al. 2007**) will be completed by the subject him/herself daily from Day -1 to Day 5 between 08:00 PM and 11:00 PM. On Day -1 and Day 0, all subjects will complete the questionnaire. From Day 1 onwards it will be completed by

subjects in the CC and THS 2.2 arms only to assess the degree to which subjects experience the reinforcing effects of smoking.

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 aware?	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.

7.3.4 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 on Day 0 to Day 6 prior to product use to reflect the previous days experience. Therefore although it is collected on Days 0 to 6 it will be reported as Days -1 to 5. Only the self-reported part of the MNWS will be used.

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 scores will be derived by summing the individual item scores if all items are non-missing, otherwise the total score will be set to missing. The first total score calculated by summing the first 9 items is based on validated items, the second score is based on 6 extra items which are thought to have an impact on withdrawal but have not been validated.

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

	Question	Total Score
1	Angry, irritable, frustrated.	1 and 2
2	Anxious, nervous.	1 and 2
3	Depressed mood, sad.	1 and 2
4	Desire or craving to smoke.	1 and 2
5	Difficulty concentrating.	1 and 2
6	Increased appetite, hungry, weight gain.	1 and 2
7	Insomnia, sleep problems, awakening at night.	1 and 2
8	Restless.	1 and 2
9	Impatient.	1 and 2
10	Constipation	2
11	Dizziness	2
12	Coughing	2
13	Dreaming or nightmares	2
14	Nausea	2
15	Sore throat	2

7.3.5 Human Smoking Topography Questionnaire

The HST questionnaire will be completed on Days 0 and 4 by all subjects smoking CC that are compatible with the HST SODIM® device (i.e., non-slim CC) to evaluate the impact of the use of the HST SODIM® device.

The HST questionnaire has 5 items rated on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree and 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.

7.3.6 Cough Assessment

Subjects will be asked to assess the respiratory symptom ‘cough’ using a VAS, three Likert scale questions, and one open ended question on a daily basis during the confinement period (on Day 0 to Day 6) prior to start of product use/smoking and no later than 10:00 AM. Although the symptoms are assessed on Days 0 to 6 the data reflects the subjects respiratory symptoms from the previous day (Days -1 to Day 5) and therefore will be reported as Days -1 to Day 5 .

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 100 mm 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**). 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 able to be processed 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	Ni	
Puff volume	Vi	mL
Puff duration	Di	S
Average flow [Vi/Di]	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	Ii	S
Sum of Ii and Di	DFi	S
Work [INT Pmi*FinalFlow*dt]	Wi	mJ
Average pressure drop	Pmi	mmWG
Peak pressure drop	Pci	mmWG
Average resistance [Pmi/Qmi]	Rmi	mmWG/mL/s
Peak resistance [Pci/Qci]	Rci	mmWG/mL/s

Table 9: HST - Per-Cigarette Parameters

Description	Variable	Formula	Unit
Total number of puffs	NPC	∑ Ni	
Total puff volume	TVOL	∑ Vi	mL
Average puff volume	AvgVi	∑ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	∑ Di / NPC, i=1 ... NPC	s
Total puff duration	TDi	∑ Di	s
Average flow	AvgQmi	∑ Qmi / NPC, i=1… NPC	mL/s
Average Peak flow	AvgQci	∑ Qci / NPC, i=1 … NPC	mL/s
Total inter puff interval	TIi	∑ Ii	s
Average inter puff interval	AvgIi	∑ Qci / NPC, i=1 … NPC	s
Total smoking duration	TDFi	∑ DFi	s
Total Work	TWi	∑Wi	mJ
Average Work	AvgWi	∑Wi / NPC, i=1 … NPC	mJ
Average pressure drop	AvgPmi	∑Pmi / NPC, i=1 … NPC	mmWg
Average Peak pressure drop	AvgPci	∑Pci / NPC, i=1 … NPC	mmWg
Smoking Intensity	SMINT	TVOL/TDFi	mL/s
Puffing Time Index	PTI	(100*TDi)/TDFi	%
Puff Frequency	PFeq	NPC/(TDFi/60)	puffs/min

7.5 Categorical Variables

The categorical variables used in this study are shown below (**Table 10**).

Table 10: Categorical Variables Definitions

Variable	Categories	
BMI (kg/m^2)	Underweight:	< 18.5[1]
	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
Daily CC consumption over the last 4 weeks as reported at Screening (per day).	<10[1]	
	10-19	
	>19	
ISO tar yields (mg)	1-5	
	6-8	
	9-10	
	>10	
CO breath test level (ppm)	≤ 10	
	> 10	
COHb level	≤ 2%	
	> 2%	

Table 10: Categorical Variables Definitions

Variable	Categories
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

[1] Note that due to inclusion criteria for the study there should not be any subjects underweight, or reporting <10 cig/day; therefore these categories will not be presented unless there is at least one response.

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 BoExp in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

Table 11 describes the expected coefficients of variation (CV) and mean ratios (MR) between THS 2.2 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 that investigated 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/CC.

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 = coefficient of variation; MHBMA = monohydroxybutenyl mercapyuric acid; MR = mean ratio; 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 and the CC 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/CC.

Table 12: Coefficients of Variation (ZRHX-EX-01 study)

	THS 2.2 /CC 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 mercapyuric acid; MR = mean ratios; S-PMA = S-phenylmercapturic acid; THS 2.2 = Tobacco Heating System 2.2.

Based on these two sets of assumptions, the power to demonstrate a reduction was computed. **Table 13** describes the expected power to demonstrate a reduction on 4 primary BoExp in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC, using one-sided test with 2.5% type I error probability using the assumptions from YVD-CS01-EU and ZRHX-EX-01 and 160 smokers (80 in THS 2.2, 40 in CC, and 40 in the SA arm).

Table 13: Expected Power (YVD-CS01-EU and ZRHX-EX-01 Studies Assumptions)

	Reduction					
Assumptions	**50%**	**51%**	**52%**	**53%**	**54%**	**55%**
YVD-CS01-EU	96%	91%	85%	75%	63%	48%
ZRHX-EX-01	>99%	>99%	96%	81%	48%	16%

A total of 160 smokers (80 in THS 2.2, 40 in CC, and 40 in the SA arm) will be randomized to demonstrate a reduction of at least 50% on 4 primary BoExp in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC, using one-sided test with 2.5% type I error probability.

The sample size is sufficient to obtain 95% CIs for the ratio between (geometrical) mean levels of primary BoExp in THS 2.2 and SA with upper and lower limits deviating not more than 18% from the point estimates, with an 80% overall probability of achieving the desired precision of estimating the true mean.

This study has 80% power using a one-sided test with 2.5% type I error probability:

1. To detect a 0.631 [mL/min/kg] (29%) difference between THS 2.2 and CC in CYP1A2 activity, as measured by the CAF clearance, assuming a standard deviation (SD) of 0.564. Effect size and variability are derived from data obtained in the YVD-CS01-EU study sponsored by PMI.
2. To detect a 24.71 [ng/g creatinine] (20%) difference between THS 2.2 and CC in 11-DTX-B2, assuming a SD of 43.78. The anticipated effect size of THS 2.2 is assumed to be about 90% of the effect of smoking cessation.

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

- Shift tables for safety endpoints will not be produced for this study, the relevant information will be provided in listings.

- Statistical analysis for blood COHb (%) and exhaled CO (ppm) measurements and the QSU-brief questionnaire data, MNWS questionnaire data and the MCEQ questionnaire data will be performed including interaction terms for product and time point to enable least square means to be calculated at each time point in order to explore the pattern of the THS 2.2 effect over time. The main comparison between products will be the comparison over all time points.

- The second exploratory objective ("To evaluate in smokers switching from CC to THS 2.2, smokers continuing smoking CC and smokers switching from CC to SA the relationship between:

- Primary and secondary BoExp and NEQ
- Selected risk markers and, primary and secondary BoExp, and NEQ

will now only investigate:

1) The relationship between primary and secondary BoExp and NEQ, which will be reported in a separate report.
2) The relationship between risk markers and NEQ, which will be reported in the CSR.

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

10 ANALYSIS POPULATIONS

The main population for non-safety analysis will be the full analysis set (FAS). The Per-Protocol (PP) Population will be used only for the analysis of the primary endpoint to examine the robustness of the primary analysis. As there is not expected to be major differences between the FAS and PP Population for this study the PP Population will only be assessed if there are more than 10 subjects excluded from the PP Population.

Safety data will be analyzed using the Safety Population.

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 or CC, and have at least one valid BoExp measurement (THS 2.2, CC, SA arms).

10.2 Per Protocol Population

The PP Population is a subset of FAS and includes all randomized subjects who:

- Have no major protocol deviation to product compliance as defined in **Table 14** if randomized to THS 2.2 or SA.
- Have not been misrandomized.
- Have no other major protocol deviation.*

*Subjects with major protocol deviations that impact the validity of the evaluation of the results (see Section **11**"**Protocol Deviations**") will be excluded in the PP Population.

10.3 Safety Population

The Safety Population consists of all the subjects who had at least one exposure to THS 2.2 (product test at Admission Day). Subjects in the Safety Population will be analyzed according to actual exposure.

11 PROTOCOL DEVIATIONS

Protocol deviations are defined as those deviations from any procedure as defined in the Study Protocol, including but not limited to, as any violation of inclusion/exclusion criteria, mis-randomizations, use of any nicotine or tobacco-containing product other than the assigned product during each of the exposure period, assessments not performed or performed outside the scheduled time windows, or 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, these will also be recorded in the EDC system.

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 Population.

11.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (at a population level) to determine whether they will be excluded from any of the analysis populations. This will take place during the pre-analysis data review meeting prior to database lock. The following have been identified as the major protocol deviations.

The categories for the major deviations will include, but are not limited to the deviations presented in **Table 14**.

Table 14: Definition of Major Protocol Deviations

Category	Description
Mis-randomization	Being administered the wrong product according to the randomization schedule.
Product compliance	Use of any nicotine or tobacco–containing product other than the assigned product. Exhaled CO breath test >10 ppm for subjects from the SA arm after Day 2
Violation	Violation of inclusion/exclusion criteria.
Duration of 24 hour collection	Start and end times not within the 30 min window.

Among the above criteria, violations of inclusion criteria 5 to 7, or of the exclusion criteria 1, 3 to 16, and 18 will be assessed for their impact on the PP Population and evaluated during the pre-analysis data review meeting (Section **6.3.1** "**Methods of Assigning Subjects to Product Arms**").

11.2 Minor Protocol Deviations

The categories for the minor deviations will include, but are not limited to the deviations presented in **Table 15**.

Table 15: Definition of Minor Protocol Deviation Categories

Category	Description
Concomitant medication	Use of drugs which are known to affect CYP2A6 or CYP1A2 activity.
Time deviation (Questionnaires)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time deviation (Blood draws)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time deviation (CYP1A2 activity)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time deviation (CYP2A6 activity)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time deviation (Assessment of cough)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time deviation (CO breath test)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time deviation (HST Recording)	Assessments not taken at the correct time or within the allowed time window (see **Table 16**)
Time missing	Assessment date or time is missing
Assessment missing	Assessment is missing
Visit missing	Scheduled visit not done

11.3 Assessment Windows

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 16**.

Table 16: Assessment Windows

Assessment	Nominal Time point(s)	Window
24 h urine sample	Start (All days) End on the following day (All days)	06:30 AM ± 20 min 06:29 AM ± 20 min
CYP1A2 activity in plasma	Start (Days 0 and 5)	6 hours after intake of caffeine tablet ± 15 min
CYP2A6 activity	Day 0 and Day 6	Prior to smoking / product use

Table 16: Assessment Windows

Assessment	Nominal Time point(s)	Window
CO breath test	Day -2 and Day 6	Irrespective of product use
	Morning (Days -1 to 5)	To be done within 15 minutes prior to product use (for THS 2.2 and CC 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
Assessment of Cough	Day 0 to 6	To be done prior to smoking/product use but not later than 10:00 AM.
MNWS Questionnaire	Day 0 to 6	To be done prior to product use but not later than 10:00 AM
QSU-brief questionnaire	Day -1 to 5	08:00 PM to 11:00 PM
MCEQ questionnaire	Day -1 to 5	08:00 PM to 11:00 PM
Nicotine and cotinine in plasma	Day 0 to Day 4 (all study arms) between 08:00 PM and 09:30 PM	
	Day 5 (THS 2.2 and CC arms) within 15 minutes before first product use (T_0): then additional blood samples at 2 hour intervals from T_0 until 11:00 PM.	Each sample has a 5 minute time window
	Day 6 (THS 2.2 and CC arms): 20 and 24 h after T_0 of Day 5	5 minute time window
	Day 5 and Day 6 (SA arm): On Day 5, between 08:00 PM and 09:30 PM. On Day 6, between 08:00 AM and 9:30 AM.	
COHb blood Sampling	Days -1 to 4	8:00 PM to 09:30 PM
	Morning sample on Day 5	Within 15 minutes prior to product use (for THS 2.2 and CC 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

Table 16: Assessment Windows

Assessment	Nominal Time point(s)	Window
HST Questionnaire	Day 0	08:00 PM-09:30 PM
	Day 4 for all subjects in the THS 2.2 and CC arms smoking compatible CC	08:00 PM-08:30 PM
HST Recording	Day 0	06:30 AM-09:30 PM
	Day 1 and Day 4 for all subjects in the THS 2.2 and CC arms smoking compatible CC	06:30 AM-09:30 PM

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Data analysis will be performed using SAS® Version 9.2 or higher.

Data listings will be provided for all data collected as required by this protocol, ordered by actual exposure and subject 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.

Safety data will be summarized for the Safety Population, biomarker data will be summarized and analyzed for the FAS unless otherwise stated.

12.1.1 Stratified Presentation

Primary BoExp summaries will be produced by arm, sex (male vs. female), CC consumption (10-19 CC/day vs. >19 CC/day) and time point (if applicable), unless otherwise stated.

12.1.2 Subgroup Analyses

No subgroup analyses will be performed in this study.

12.1.3 Descriptive Statistics

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic SD, median, first and third quartiles, minimum, maximum, and number; for log-normal data the geometric mean and geometric CV will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will include all subject level data collected unless otherwise specified. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Summaries on the Safety Population will be produced by actual exposure, including the additional set of subjects who tested the product but were not enrolled or were discontinued from enrollment before randomization.

The following product labels will be used throughout the TFLs (**Table 17**):

Table 17: Product Labels

Product	Format used in TFLs	Order in TFLs
Tobacco Heating System 2.2	THS 2.2	1
Conventional cigarettes	CC	2
Smoking abstinence	SA	3

The following stratification labels (**Table 18**) for the TFLs will be used:

Table 18: Stratification Labels

Stratification Factor	Definition
Sex	male female
Daily CC consumption (per day)	<10[1] 10-19 >19

[1] Note that due to inclusion criteria for the study there should not be any subjects with CC consumption <10, therefore this category will not be presented unless there is sufficient data for analysis/presentation (see Section **12.1.5.1** "**Insufficient Data for Analysis/Presentation**").

12.1.4 Definitions for Statistical Data Analysis

The following definitions (**Table 19**) for statistical analyses/presentations will be used:

Table 19: Definition of terms for the statistical analysis

Term	Definition
Baseline Value	The last assessment prior to 06:29 AM on Day 1

N.B. For data where baseline is different to the above will be defined in the specific section of the SAP.

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, i.e., Day 5, in the SAP.

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

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

total scores and domain or subscale scores may use a certain degree of imputation (by averaging across individual item scores) as detailed in Section **7.3** "**Questionnaires**".

Laboratory parameters will be presented as detailed in Section **7.1** "**Biomarkers**".

12.1.5.1 Insufficient Data for Analysis/Presentation

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

Some of the TFLs will 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 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 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

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, and discontinued (if applicable discontinued subject that never used their allocated products will be identified).

Subjects in the Safety Population will be displayed by actual exposure.

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 actual exposure. Disposition of subjects and reasons for withdrawal will also be summarized separately. Supportive listings will be provided.

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

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, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.1.1	Summary of Subject Disposition – All Screened Subjects
15.2.1.2	Summary of Reasons for Discontinuations – All Randomized Subjects
15.2.1.3	Summary of Protocol Deviations – Safety Population
LISTINGS	
15.3.1.1	Listing of Inclusion/Exclusion Criteria
15.3.1.10	Listing of Subject Disposition, Randomization and Assignment to Analysis Sets
15.3.1.13	Listing of Protocol Deviations
15.3.2.7	Listing of Subject and Observations Excluded from Efficacy Analysis
16.1.7	Listing of Randomization Schemes and Codes

12.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population and FAS, and listed for all screened subjects.

The demographic variables age, sex, race, body weight, height and BMI will be summarized by actual exposure, and by the two stratification factors (sex, and CC 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, the TFL number refers to the TFL number in the accompanying TFL shell document:

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

TFL number	Title
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – FAS
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS
LISTINGS	
15.3.1.9	Listing of Demographics

12.3.1 FTND Questionnaire at Screening

FTND score value and the number and percentage of subjects in each category (mild/moderate/severe) will be presented. Data will be listed and summarized as reported in Section **12.3** "**Demographics and Other Baseline Characteristics**".

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

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
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – FAS
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS
LISTINGS	
15.3.1.12	Listing of Fagerström Test for Nicotine Dependence Results

12.3.2 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), and number of CCs smoked on a daily basis during the previous 4 weeks (continuous and categorized as 10-19 CC/day and >19 CC/day).

Current CC brand(s) smoked by the subject and recorded at the Screening Visit and Admission (Day -2) will be summarized and listed by actual exposure and study day for the Safety Population. This will include brand name(s) and ISO nicotine, tar, and CO yields. Data at screening will be listed only.

Smoking history, including whether subjects have smoked for at least the last three consecutive years and whether the subject smoked any mentholated CCs during the previous 4 weeks will be listed by actual exposure at Screening and Admission (Day -2) where applicable. Responses to planning to quit smoking during the next 3 months will be

listed at Screening. Readiness to accept interruption of smoking for up to 5 days and the advice on the risks of smoking and debriefing will be listed at Admission.

Data will be listed and summarized as presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

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
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – FAS
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS
15.2.1.5	Summary of Current Cigarette Brands – Safety Population
LISTINGS	
15.3.1.2	Listing of Current Cigarette Brands
15.3.1.3	Listing of Smoking History
15.3.1.5	Listing of Advice on Risks of Smoking
15.3.1.6	Listing of Willingness to Abstain from Smoking During the Next 3 Months
15.3.1.7	Listing of readiness to Accept Interruption of Smoking for up to 5 days

12.3.3 Medical History and Concomitant Diseases

Medical history is defined as any condition that started and ended prior to Screening. Medical history will be coded using MedDRA version 16.0 and listed separately by actual exposure, System Organ Class (SOC) and Preferred Term (PT) within SOC.

Medical History will be summarized by actual exposure, SOC and PT for the FAS.

Concomitant disease is defined as any condition diagnosed at Screening or was ongoing at Screening. Concomitant disease will be coded using MedDRA version 16.0 and listed separately by actual exposure, SOC and PT within SOC.

Concomitant disease will be summarized by actual exposure, SOC and PT for the Safety Population.

Partial dates will not be imputed, but assumptions will be made as follows to assign to either medical history or concomitant diseases:

Date information	Assign as
Missing stop date	Concomitant disease
Partial date, e.g. --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Screening.	Concomitant disease
Partial date, e.g. --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening.	Medical history

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.1.6	Summary of Medical History – Safety Population
15.2.1.7	Summary of Concomitant Diseases – Safety Population
LISTINGS	
15.3.1.11	Listing of Medical History and Concomitant Diseases

12.3.4 Other Data

Other data collected at Screening and/or Admission will be listed by actual exposure. 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
- Debriefing and risk of smoking
- Willingness to use THS 2.2

Willingness and ability to use the products will also be summarized.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.10.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.10.2	Summary of Prior Medication by Preferred Term – Safety Population
LISTINGS	
15.3.1.4	Listing of Product Test and Willingness to Use the Product
15.3.1.8	Listing of Safety Laboratory Entry Criteria
15.3.6.3	Listing of Prior and Concomitant Medication

12.4 Measurements of Product Compliance

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

In addition, 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 during the confinement period. These data (continuous and categorical) will be summarized and listed by actual exposure.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.5.1	Summary of Compliance as Measured by Exhaled CO (ppm) in the SA Arm- Safety Population
LISTINGS	
15.3.3.2	Listing of Secondary Biomarkers and Sampling/Collection Times

12.5 Extent of Exposure (Product Consumption)

Details of the product test prior to enrollment and of daily product use after randomization will be listed and summarized.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.2.1	Summary of Use of THS 2.2 Product and CC – Safety Population
LISTINGS	
15.3.2.1	Listing of Product Usage
15.3.2.2	Listing of Cigarette Butt and THS Tobacco Stick Collection Data

12.6 Planned Statistical Analyses

Markedly non-lognormally distributed BoExp data will be transformed or analyzed by appropriate non-parametric methods with bootstrapping using the SAS procedure PROC SURVEYSELECT. The seed to be used in any analysis will be contained in the SAS output and will be different for each analysis.

For all statistical analysis data from all arms, THS 2.2, CC and SA will be included in all models.

12.6.1 Primary Analyses

12.6.1.1 Primary Biomarkers of Exposure in 24 hour collection

The primary BoExp (COHb in blood and urinary concentrations adjusted for creatinine of MHBMA, 3-HPMA and S-PMA) will be summarized as detailed in Section **12.1.3** "**Descriptive Statistics**".

The baseline is as defined in Section **12.1.4** "**Definitions for Statistical Data Analysis**",

The values and percent changes in the concentration adjusted for creatinine will be listed and summarized along with the COHb concentrations and percent changes from baseline. In addition line graphs will be produced for means (and 95% CI) over all timepoints.

For all arms the 24 hour urine collection will be collected daily from Day -1 to Day 5. Although the 24 hour urine collection will span into the following Day it will be reported by the day the collection started.

The primary endpoints will be log-transformed ($base_e$) prior to analysis. The analysis will compare (1) last Day 5 values of COHb in blood and (2) urinary concentrations of MHBMA, 3-HPMA and S-PMA corrected for creatinine on Day 5 between the THS 2.2 and CC arms. An ANCOVA (**Snedecor and Cochran 1982**) model will be used with terms for the log-transformed baseline value, sex, average daily CC consumption over the last 4 weeks as reported during screening and product.

The SAS code to be used is shown below:

```
Proc mixed data=_data_;
Class product sex cigarette_cons;
Model log (Day 5) = log (baseline) sex cigarette_cons product;
Lsmean product / pdiff =control('CC') alpha=0.05 cl;
Run;
```

The least squares (LS) means and estimate of the difference along with it's 95% CI will be back-transformed before presenting in the tables. The geometric LS means for each product along with the ratio (THS 2.2 : CC) and 95% CI will be presented in the tables.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.1.1	Blood COHb (%) Mean and 95% CI– FAS
15.1.1.2	MHBMA Urinary Concentration Adjusted for Creatinine (units) Mean and 95% CI – FAS
15.1.1.3	3-HPMA Urinary Concentration Adjusted for Creatinine (units) Mean and 95% CI– FAS
15.1.1.4	S-PMA Urinary Concentration Adjusted for Creatinine (units) Mean and 95% CI– FAS
15.1.1.5	Blood COHb (%) % Change from Baseline Mean and 95% CI– FAS
15.1.1.6	MHBMA Urinary Concentration Adjusted for Creatinine (units) % Change from Baseline Mean and 95% CI – FAS
15.1.1.7	3-HPMA Urinary Concentration Adjusted for Creatinine (units) % Change from Baseline Mean and 95% CI– FAS
15.1.1.8	S-PMA Urinary Concentration Adjusted for Creatinine (units) % Change from Baseline Mean and 95% CI– FAS
TABLES	
15.2.3.1	Analysis of Blood COHb (%) versus CC on Day 5 – FAS
15.2.3.2	Analysis of MHBMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – FAS
15.2.3.3	Analysis of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – FAS
15.2.3.4	Analysis of S-PMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – FAS
15.2.3.5	Descriptive Statistics of % Change in Primary Biomarkers of Exposure on Day 5 – FAS
15.2.3.5.1	Descriptive Statistics of % Change in Primary Biomarkers of Exposure on Day 5 by Sex – FAS

TFL number	Title
15.2.3.5.2	Descriptive Statistics of % Change in Primary Biomarkers of Exposure on Day 5 by Cigarette Consumption – FAS
15.2.3.6	Descriptive Statistics of Blood COHb (%) – FAS
15.2.3.6.1	Descriptive Statistics of Blood COHb (%) by Sex – FAS
15.2.3.6.2	Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – FAS
15.2.3.7	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) – FAS
15.2.3.7.1	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS
15.2.3.7.2	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS
15.2.3.8	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) – FAS
15.2.3.8.1	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS
15.2.3.8.2	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS
15.2.3.9	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) – FAS
15.2.3.9.1	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS
15.2.3.9.2	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS
LISTINGS	
15.3.3.1	Listing of Primary Biomarkers

The listing of the urinary biomarkers will include the concentration, the percent change in the concentration, the concentration adjusted for creatinine, the percent change in the concentration adjusted for creatinine, the volume of urine in the 24 hour collection, the quantity excreted over 24 hours and the percent change in quantity excreted over 24 hours.

The listing of the COHb data will include the concentration, the percent change in the concentration, and a flag for whether a subject's COHb is <2%.

12.6.1.2 Confirmatory Analysis

The hypothesis to be tested for each of the primary BoExp is that the geometric mean level on Day 5 of the BoExp for THS 2.2 is lower relative to CC.

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

Null hypothesis (H_0): $m1 \geq m2$

Alternative hypothesis (H_1): m1<m2

Where m1 and m2 are the geometric means of the BoExp levels on Day 5 for THS 2.2 and CC respectively.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**".

The confirmatory analysis will be performed on the FAS only. However, if the PP and FAS differ by more than 10 subjects then the analysis will be repeated for the PP population.

12.6.2 Secondary Analyses

12.6.2.1 Biomarkers of Exposure

In addition, the quantity excreted over 24 hours for MHBMA, 3-HPMA and S-PMA will be presented.

The PP Population will be used to examine the robustness of the analysis of the primary endpoints. The primary analysis on the FAS will be repeated on the PP population using the same methodology as detailed in Section 12.6.1.1 "Primary Biomarkers of Exposure in 24 hour collection".

The primary BoExp will also be examined to compare the reductions in THS 2.2 vs. SA using the same methodology as for the primary analysis.

The secondary BoExp are exhaled CO, total 1-OHP in urine, Total NNN in urine, 4-ABP in urine, 1-NA in urine, 2-NA in urine, o-tol in urine, CEMA in urine, HEMA in urine, B[a]P in urine, HMPMA in urine, S-BMA in urine, Total NNAL in urine and NEQ in urine. The urine parameters will be expressed as concentrations adjusted for creatinine and the quantity excreted over 24 hours.

The baseline of the exhaled CO will be the time-matched measurements on Day 0, i.e. the 1st measurement on Days 1 to 5 will be matched to the 1st measurement on Day 0 and similarly for the 2nd, 3rd and 4th measurements. The baseline of the urinary biomarkers will be the last assessment prior to 06:29 AM on Day 1.

The values and percent changes for urinary BoExp in the quantity excreted over 24-hours and the concentration adjusted for creatinine will be listed and summarized. In addition line graphs will be produced for product means (and 95% CI) over all timepoints.

CO in exhaled breath will be measured using the Micro+™ Smokerlyzer® or similar device, conducted on Day -2 to Day 6. On Day -1 to Day 5 the first test per day will be performed within 15 minutes prior to the first product use and then between 12:00 and 01:30 PM, between 04:00 and 05:30 PM and between 08:00 and 09:30 PM. On Days -2 and Day 6 the CO breath tests will be conducted once.

Descriptive statistics summarized by exposure will be produced separately for all timepoints for all visits applicable for exhaled CO. This will be done on the FAS, stratified by sex, and CC consumption.

Actual values and percent changes from baseline in levels of exhaled CO will be listed and summarized. In addition line graphs will be produced for product means (and 95% CI) over all timepoints.

The last measurement of exhaled CO will be used in the analyis. An ANCOVA model will be used with terms for the baseline value, sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

The analysis will compare the log-transformed urinary concentrations corrected for creatinine on Day 5 to 6 and the quantity excreted over 24-hours on Day 5 to 6 between the THS 2.2 and CC arms. An ANCOVA model will be used with terms for the log-transformed baseline value, sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**".

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

The secondary BoExp will also be examined to compare the reductions in THS 2.2 vs. SA using the same methodology as above.

TFL number	Title
FIGURES	
15.1.2.1	Urinary MHBMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.2	Urinary 3-HPMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.3	Urinary S-PMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.4	Exhaled CO Arithmetic Mean and 95% CI– FAS
15.1.2.5	1-OHP Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.6	Urinary 1-OHP Quantity excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.7	Total NNN Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.8	Urinary Total NNN Quantity Excreted Over 24 hours Mean and 95% CI– FAS

TFL number	Title
15.1.2.9	4-ABP Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.10	Urinary 4-ABP Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.11	1-NA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.12	Urinary 1-NA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.13	2-NA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.14	Urinary 2-NA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.15	o-tol Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.16	Urinary o-tol Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.17	CEMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.18	Urinary CEMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.19	HEMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.20	Urinary HEMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.21	B[a]P Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.22	Urinary B[a]P Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.23	3-HMPMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.24	Urinary 3-HMPMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.25	S-BMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.26	Urinary S-BMA Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.27	Total NNAL Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.28	Urinary Total NNAL Quantity Excreted Over 24 hours Mean and 95% CI– FAS
15.1.2.29	NEQ Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.2.30	Urinary NEQ Quantity Excreted Over 24 hours Mean and 95% CI– FAS
TABLES	
15.2.4.1	Analysis of Blood COHb (%) versus CC on Day 5 – PP Population
15.2.4.2	Analysis of MHBMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – PP Population

TFL number	Title
15.2.4.3	Analysis of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – PP Population
15.2.4.4	Analysis of S-PMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – PP Population
15.2.4.5	Analysis of Primary Biomarkers of Exposure versus SA on Day 5 – FAS
15.2.4.6	Analysis of Urinary Quantity Excreted of MHBMA, 3-HPMA and S-PMA over 24 hours on Day 5 – FAS
15.2.4.7	Descriptive Statistics of Urinary Quantity Excreted of MHBMA over 24 hours (units) – FAS
15.2.4.8	Descriptive Statistics of Urinary Quantity Excreted of 3-HPMA over 24 hours (units) – FAS
15.2.4.9	Descriptive Statistics of Urinary Quantity Excreted of S-PMA over 24 hours (units) – FAS
15.2.4.10	Analysis of Exhaled CO (ppm) on Day 5 – FAS
15.2.4.11	Descriptive Statistics of Exhaled CO (ppm) – FAS
15.2.4.12	Descriptive Statistics of Time Matched Changes (%) in Exhaled CO – FAS
15.2.4.13	Analysis of Urinary 1-OHP on Day 5 – FAS
15.2.4.14	Descriptive Statistics of Urinary 1-OHP – FAS
15.2.4.15	Analysis of Urinary Total NNN on Day 5 – FAS
15.2.4.16	Descriptive Statistics of Urinary Total NNN – FAS
15.2.4.17	Analysis of Urinary 4-ABP on Day 5 – FAS
15.2.4.18	Descriptive Statistics of Urinary 4-ABP – FAS
15.2.4.19	Analysis of Urinary 1-NA on Day 5 – FAS
15.2.4.20	Descriptive Statistics of Urinary 1-NA – FAS
15.2.4.21	Analysis of Urinary 2-NA on Day 5 – FAS
15.2.4.22	Descriptive Statistics of Urinary 2-NA – FAS
15.2.4.23	Analysis of Urinary o-tol on Day 5 – FAS
15.2.4.24	Descriptive Statistics of Urinary o-tol – FAS
15.2.4.25	Analysis of Urinary CEMA on Day 5 – FAS
15.2.4.26	Descriptive Statistics of Urinary CEMA – FAS
15.2.4.27	Analysis of Urinary HEMA on Day 5 – FAS
15.2.4.28	Descriptive Statistics of Urinary HEMA – FAS
15.2.4.29	Analysis of Urinary B[a]P on Day 5 – FAS
15.2.4.30	Descriptive Statistics of Urinary B[a]P – FAS
15.2.4.31	Analysis of Urinary HMPMA on Day 5 – FAS
15.2.4.32	Descriptive Statistics of Urinary HMPMA – FAS
15.2.4.33	Analysis of Urinary S-BMA on Day 5 – FAS
15.2.4.34	Descriptive Statistics of Urinary S-BMA – FAS
15.2.4.35	Analysis of Urinary Total NNAL on Day 5 – FAS
15.2.4.36	Descriptive Statistics of Urinary Total NNAL – FAS
15.2.4.37	Analysis of Urinary NEQ on Day 5 – FAS
15.2.4.38	Descriptive Statistics of Urinary NEQ – FAS

TFL number	Title
LISTINGS	
15.3.3.2	Listing of Secondary Biomarkers and Sampling / Collection Times

12.6.2.1.1 Confirmatory Analysis

The hypothesis to be tested for each of the secondary BoExp is that the geometric mean level on Day 5 of the BoExp for THS 2.2 is lower relative to CC.

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

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

Where m1 and m2 are the geometric means of the BoExp levels on Day 5 for THS 2.2 and CC respectively.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**".

12.6.2.2 Nicotine and Cotinine Concentrations

The change from the Day 0 sample will be calculated for the Day 5 sample closest to 08:00 PM only. The concentrations of nicotine and cotinine will be listed and summarized along with this change. Line graphs of the nicotine and cotinine concentration profiles across all study days showing mean and 95% CI will also be produced.

For nicotine and cotinine plasma concentrations the change from baseline (Day 0 sample at 08:00 PM - 09:30 PM)) on the Day 5 sample closest to 08:00 PM will be analyzed using an ANCOVA model with terms for baseline (Day 0) concentration, sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

The SAS code to be used is shown below:

```
Proc mixed data=_data_;
Class product sex cigarette_cons time_point;
Model change from baseline = baseline sex cigarette_cons product;
Lsmean product / diff alpha=0.05 cl;
Run;
```

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

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.2.31	Plasma Nicotine Concentrations (ng/mL) Mean and 95% CI on Day 5 – FAS
15.1.2.32	Plasma Cotinine Concentrations (ng/mL) Mean and 95% CI on Day 5 – FAS
TABLES	
15.2.4.40	Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) – FAS
15.2.4.41	Descriptive Statistics of Plasma Cotinine Concentrations (ng/mL) – FAS
15.2.4.46	Analysis of Change from Day 0 Plasma Nicotine and Cotinine Concentrations at 08:00 PM on Day 5 – FAS
LISTINGS	
15.3.3.4	Listing of Plasma Nicotine Concentrations and Sampling Times
15.3.3.5	Listing of Plasma Cotinine Concentrations and Sampling Times

12.6.2.3 Nicotine and Cotinine Pharmacokinetic Parameters

The parameters C_{peak}, C_{avg} and t_{peak} will be determined 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 C_{peak} and C_{avg} on Day 5 between the THS 2.2 and CC arms. An analysis of variance (ANOVA) model will be used with terms for sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

The SAS code will be similar to that described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**", with no baseline value being included in the model.

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

For t_{peak} on Day 5 the comparison between the THS 2.2 and CC arms will be made by the Wilcoxon Rank Sum test using PROC NPAR1WAY in SAS.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.4.42	Descriptive Statistics of Plasma Nicotine Concentration Parameters on Day 5 – FAS
15.2.4.43	Descriptive Statistics of Plasma Cotinine Concentration Parameters on Day 5 – FAS

TFL number	Title
15.2.4.44	Analysis of Plasma Nicotine Concentration Parameters on Day 5 – FAS
15.2.4.45	Analysis of Plasma Cotinine Concentration Parameters on Day 5 – FAS
LISTINGS	
15.3.3.6	Listing of Plasma Nicotine Concentration Parameters on Day 5
15.3.3.7	Listing of Plasma Cotinine Concentration Parameters on Day 5

12.6.2.4 CYP1A2 Activity

CYP1A2 activity will be measured in plasma on Day 0 and Day 5. In this study the CYP1A2 activity will be calculated using the molar ratio of PX and CAF, as described in Section **7.1.4** "**CYP1A2**". Descriptive statistics of the values and percent change on Day 5 from Day 0 and supportive listings will be provided.

The analysis will compare the Day 5 values between the THS 2.2 and CC arms and between the THS 2.2 and SA arms. An ANOVA model will be used with terms for sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**", with no baseline value being included in the model.

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

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.4.54	Descriptive Statistics of CYP1A2 Activity (%) – FAS
15.2.4.55	Analysis of CYP1A2 Activity (%) on Day 5– FAS
LISTINGS	
15.3.4.1	Listing of CYP1A2 Activity and Changes from Baseline

12.6.3 Exploratory Analysis

12.6.3.1 Questionnaires

12.6.3.1.1 Urge-to-Smoke Questionnaire of Smoking Urges Brief

The QSU-brief will be administered daily from Days -1 to 5. The baseline will be the last assessment prior to 06:29 AM on Day 1.

All summaries, profiles and analysis will be presented for the THS 2.2, CC and SA arms.

The change from baseline will be calculated for the total score and the two domain scores (relief and reward). The total score and two domain scores, along with the change from baseline will be summarized. The answers to the individual questions, along with the domain scores, total scores and changes from baseline will be listed.

The profiles of the raw means from baseline to Day 5 for the total score and two domain scores will be produced.

The analysis will compare each post baseline timepoint in the domain and total scores. A repeated measures ANCOVA model will be used with terms for baseline QSU-BRIEF score, sex, average daily CC consumption over the last 4 weeks as reported during screening, product, timepoint, and the interaction between product and timepoint. No adjustment will be made for multiple comparisons.

The SAS code to be used is shown below:

```
Proc mixed data=_data_;
Class product sex cigarette_cons time_point;
Model reduction = base_QSU sex cigarette_cons product
product*time_point;
Repeated time_point / subject=subject type=un;
Lsmean product / diff alpha=0.05 cl;
Run;
```

LS means for each product along with the difference (THS 2.2 - CC) and (THS 2.2 – SA) with 95% CI will be presented in the tables. The SAS code above will also be amended appropriately to obtain the right comparisons.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.2.33	QSU-brief Factors and Total Scores Arithmetic Mean and 95% CI– FAS
15.1.2.34	QSU-brief Factors and Total Scores Arithmetic Least Squares Mean Differences and 95% CI – FAS
TABLES	
15.2.4.48	Descriptive Statistics of QSU-brief Factors and Total Scores – FAS
15.2.4.49	Analysis of QSU-brief Factors and Total Scores – FAS
LISTINGS	
15.3.6.11	Listing of QSU-brief Questionnaire Results and Changes from Baseline

12.6.3.1.2 Modified Cigarette Evaluation Questionnaire

The MCEQ will be administered daily from Days -1 to 5. The baseline will be the last assessment prior to 06:29 AM on Day 1.

All summaries, profiles and analysis will be presented for the THS 2.2 and CC only. The MCEQ is not captured for the SA arm.

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

The profiles of the raw means from baseline to Day 5 for the five subcale scores will be produced.

The analysis will compare each post baseline timepoint in the subscales. A repeated measures ANOVA model will be used with terms for baseline MCEQ score, sex, average daily CC consumption over the last 4 weeks as reported during screening, product, time-point, and the interaction between product and time-point. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in Section **12.6.3.1.1** "**Urge-to-Smoke Questionnaire of Smoking Urges Brief**".

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

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.2.38	MCEQ Subscales Arithmetic Mean and 95% CI– FAS
15.1.2.39	MCEQ Subscales Arithmetic Least Squares Mean Differences and 95% CI – FAS
TABLES	
15.2.4.52	Descriptive Statistics of MCEQ Subscales – FAS
15.2.4.53	Analysis of MCEQ Subscales – FAS
LISTINGS	
15.3.6.13	Listing of MCEQ Questionnaire Results and Changes from Baseline

12.6.3.1.3 Minnesota Nicotine Withdrawal Questionnaire

The MNWS will be administered daily from Days 0 to 6 for the assessment of Day-1 to Day 5 as it is a 24-hour recall questionnaire. The baseline will be the last assessment prior to 06:29 AM on Day 1.

All summaries, profiles and analysis will be presented for the THS 2.2, CC and SA arms.

The change from baseline will be calculated for both scores. The two scores, along with the change from baseline will be summarized. The answers to the individual questions, along with the two scores and changes from baseline will be listed.

The profiles of the raw means from baseline to Day 5 for the total scores will be produced.

The analysis will compare each post baseline timepoint for the two scores. A repeated measures ANCOVA model will be used with terms for baseline score, sex, average daily CC consumption over the last 4 weeks as reported during screening, product, time-point, and the interaction between product and time-point. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in Section **12.6.3.1.1** "**Urge-to-Smoke Questionnaire of Smoking Urges Brief**".

LS means for each product along with the difference (THS 2.2 - CC) and (THS 2.2 – SA) with 95% CI will be presented in the tables. The SAS code above will also be amended appropriately to obtain the right comparisons.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.2.35	MNWS Total Scores Arithmetic Mean and 95% CI– FAS
15.1.2.36	MNWS Total Scores Arithmetic Least Squares Means and 95% CI– FAS
TABLES	
15.2.4.50	Descriptive Statistics of MNWS Total Scores – FAS
15.2.4.51	Analysis of MNWS Total Scores – FAS
LISTINGS	
15.3.6.12	Listing of MNWS Questionnaire Results and Changes from Baseline

12.6.3.2 Human Smoking Topography Parameters

The HST assessments will take place on Day 0, Day 1 and Day 4 in the THS 2.2 and CC arms only, if CC are compatible with the HST SODIM® device.

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 summarized along with their changes from baseline. The per-puff and per-cigarette parameters will be listed. In addition the product mean and 95% CI per cigarette parameters will be presented graphically.

The per-cigarette parameters will be analyzed on Days 1 and 4 separately using an ANCOVA model on the log-transformed HST parameter with terms for log-transformed baseline score, sex, average daily CC consumption over the last 4 weeks as reported during screening, product. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**".

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

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.2.39	HST per Cigarette Parameters Arithmetic Mean and 95% CI– FAS
TABLES	
15.2.4.63	Descriptive Statistics of HST Parameters per Cigarette – FAS
15.2.4.64	Analysis of HST per Cigarette – FAS
LISTINGS	
15.3.7.1	Listing of HST Assessments

12.6.3.3 Human Smoking Topography Questionnaire

The HST questionnaire will be administered on Days 0 and 4.

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, the TFL number refers to the TFL number in the accompanying TFL shell document:

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

12.6.3.4 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Days 0 and 6. In this study the CYP2A6 activity will be calculated using the metabolic ratio of trans 3' hydroxycotinine and cotinine, as described in Section **7.1.5** "**CYP2A6**". Descriptive statistics of the values and change on Day 6 from Day 0 and supportive listings will be provided.

The analysis will compare the Day 6 values (both absolute and change from baseline) between the THS 2.2 and CC arms between the THS 2.2 and SA arms. An ANCOVA model will be used with terms for baseline, sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**".

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

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.4.56	Descriptive Statistics of CYP2A6 Activity (%) – FAS
15.2.4.57	Analysis of CYP2A6 Activity – FAS
LISTINGS	
15.3.6.15	Listing of CYP2A6 Activity and Changes from Baseline

12.6.3.5 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**".

12.6.3.6 Risk Markers

The risk markers are 8-epi-PGF2α and 11-DTX-B2 in urine and will be presented as quantity excreted over 24 hours and concentration adjusted for creatinine.

The quantity excreted over 24 hour, percent changes in the quantity excreted and the concentration adjusted for creatinine in 24 hour urine 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 concentrations adjusted for creatinine and the quantity excreted over 24 hour on Day 5 between the THS 2.2 and CC arms, and between the THS 2.2 and SA arms. An ANCOVA model will be used with terms for Day 0 concentration adjusted for creatinine or quantity excreted over 24 hours, sex, average daily CC consumption over the last 4 weeks as reported during screening and product. No adjustment will be made for multiple comparisons.

If there is evidence of non-normality (see Section **12.6**, "**Planned Statistical Analyses**" then the concentrations or quantity excreted will be transformed prior to analysis.

The SAS code will be the same as described in Section **12.6.1.1** "**Primary Biomarkers of Exposure in 24 hour collection**".

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.4.58	Analysis of Urinary 8-epi-PGF2α on Day 5 – FAS
15.2.4.59	Descriptive Statistics of Urinary 8-epi-PGF2α – FAS
15.2.4.60	Analysis of Urinary 11-DTX-B2 on Day 5 – FAS
15.2.4.61	Descriptive Statistics of Urinary 11-DTX-B2 – FAS
LISTINGS	
15.3.3.3	Listing of Risk Markers and Collection Times

12.6.3.6.1 Relationship Between Risk Markers, BoExp and NEQ

The relationship between risk markers and BoExp will not be reported as stated in Section **9** "**CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS**".

The relationship between risk markers, and NEQ will be examined by fitting a general linear model (glm) with terms for baseline and Day 5 NEQ for each treatment arm separately. The SAS code to be used is as shown below:

```
Proc glm data=_data_;
Model Risk marker = baseline NEQ Day 5 NEQ;
Run;
```

The slope along with 95% CIs and the p-value will be presented for each analysis.

In addition scatterplots of each risk marker separately with NEQ, with the regression from the above model shown on the plot if there was a significant slope from the above model.

In these plots the risk marker will be on the y-axis.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
FIGURES	
15.1.2.40	Scatterplot of 8-epi-PGF2α Urinary Concentration Adjusted for Creatinine vs. NEQ Urinary Concentration Adjusted for Creatinine – FAS
15.1.2.41	Scatterplot of Urinary 8-epi-PGF2α Quantity Excreted over 24 hours vs. Urinary NEQ Quantity Excreted over 24 hours – FAS
15.1.2.42	Scatterplot of 11-DTX-B2 Urinary Concentration Adjusted for Creatinine vs. NEQ Urinary Concentration Adjusted for Creatinine – FAS
15.1.2.43	Scatterplot of Urinary 11-DTX-B2 Quantity Excreted over 24 hours vs. Urinary NEQ Quantity Excreted over 24 hours– FAS
TABLES	
15.2.4.62	Statistical Analysis of the Relationship Between Risk Markers and NEQ – FAS

12.6.3.7 Ames Mutagenicity Test

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

Descriptive statistics of the values and change on Day 5 from Day 0 of the YG1024+S9 mutagenicity will be provided, along with listings.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.4.47	Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (units) – FAS
LISTINGS	
15.3.5.1	Listing of Mutagenicity Results and Changes from Baseline

12.6.3.8 Visual Inspection of the Tobacco Plugs

The collection of the tobacco plugs from the THS 2.2 products will be performed on Days 1 to 5. 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.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.4.66	Descriptive Statistics of Visual Inspection of the THS 2.2 Tobacco Plugs Data – FAS
LISTINGS	
15.3.6.16	Listing of Visual Inspection of the Tobacco Plugs Results

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).

The primary analysis of Safety parameters will be conducted on the Safety Population as described in Section **12.1.3** "**Descriptive Statistics**".

12.6.4.1 Safety Reporting

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

All AEs occurring from the time of signing of informed consent will be recorded electronically. However, during the screening period (prior to first product use), only study related 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).

AEs reported for subjects that have a first product use, but were not randomized will be summarized in a separate group: “Exposed but not randomized”.

Partial dates will not be imputed, but assumptions will be made as follows to assign to product-emergent or not:

Date information	Assign as
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
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

12.6.4.2 Adverse Events

12.6.4.2.1 All Adverse Events

All AE tables will be presented by actual exposure.

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 / CC) and expectedness (expected for THS 2.2 / CC).
- 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 system organ class (SOC) and preferred term (PT) coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 16.0):

- 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 with at least one AE related to product exposure and expectedness for investigational product (IP; THS 2.2 or CC).
- The number of events and the number and percentage of subjects with at least one AE leading to product discontinuation or reduction.
- The number of events and the number and percentage of subjects with at least one AE leading to study discontinuation.
- The number of events and the number and percentage of subjects with at least one AE related to study procedure.
- The number of events and the number and percentage of subjects with at least one AE by severity (mild, moderate, severe).

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 = severe, for presentation by relationship = related). Missing information on the intensity of AE will be counted as severe.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.1	Summary of Adverse Events – Safety Population
15.2.6.2.1	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.2.2	Summary of Adverse Events by System Organ Class – Safety Population
15.2.6.2.3	Summary of Adverse Events by Preferred Term – Safety Population
15.2.6.3	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure for Investigational Product (THS 2.2 or CC) and Expectedness – Safety Population
15.2.6.4	Summary of Adverse Events Leading to Investigational Product (THS 2.2 or CC) Discontinuation or Reduction by System Organ Class and Preferred Term – Safety Population
15.2.6.5	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.6	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population
15.2.6.7	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.8	Summary of Serious Adverse Events – Safety Population
LISTINGS	
15.3.6.1.1	Listing of Adverse Events

12.6.4.2.2 Serious Adverse Events (Including Deaths)

A general summary table of SAEs will be presented using the same approach of AEs (see Section **12.6.4.2** "**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 a separate listing by actual exposure.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.8	Summary of Serious Adverse Events – Safety Population
15.2.6.9	Summary of Serious Adverse Events by System Organ Class and Preferred Term – 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 actual exposure as described in Section **12.6.4.2** "**Adverse Events**",

AEs leading to withdrawal will also be listed in a separate listing by actual exposure.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.5	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
LISTINGS	
15.3.6.1.3	Listing of Adverse Events Leading to Study Discontinuation

12.6.4.2.4 Laboratory Abnormalities

Laboratory abnormality data will be listed ordered by actual exposure, subject, parameter and time point. Details related to the toxicity grading of laboratory abnormalities are available in Section **12.6.4.4** "**Clinical Laboratory Evaluation**".

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
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

12.6.4.3 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 **C54451/Medical_Device_Problem_Codes_FDA_CDRH**.

A summary table of device events will be presented by actual exposure, 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 (Cigarette Holder (CH) stops heating, CH does not charge, CH led blinking red, Smoking experience does not start, electronic malfunction, other).

Device events and inventory will be listed by actual exposure. Data collected during Screening will be listed but not summarized.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.9	Summary of THS 2.2 Device Events and Malfunctions – Safety Population
LISTINGS	
15.3.6.2	Listing of THS 2.2 Device Events and Malfunctions

12.6.4.4 Clinical Laboratory Evaluation

Table 20 below lists the hematology, clinical chemistry and urine analysis parameters to be assessed in this study.

Table 20: List of Laboratory Safety Parameters

Hematology	Clinical chemistry	Urine analysis
Haematocrit	Albumin	pH
Haemoglobin	Total protein	Bilirubin
Mean corpuscular haemoglobin	Alkaline phosphatase	Glucose
	Alanine aminotransferase	Nitrite
Mean corpuscular haemoglobinconcentration	Aspartate aminotransferase	Red blood cell traces
	Blood urea nitrogen	Protein
Mean corpuscular volume	Creatinine	Specific gravity
Platelet count	Gamma-glutamyltransferase	
Red blood cell count	Fasting glucose	
White blood cell (WBC) count	Lactate dehydrogenase	
Differential WBC count:	Potassium	
• Neutrophils	Sodium	
• Basophils	Total bilirubin	
• Eosinophils	Direct bilirubin	
• Lymphocytes	Total cholesterol	
• Monocytes	Triglycerides	

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for its clinical relevance. If the Investigator 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 Investigator to assess abnormal laboratory results. These CTCAE grades will be derived programmatically in the creation of the datasets.

Laboratory data will be summarized at Screening, Day 0 and at Day of Discharge (Day 6 or day of withdrawal), together with changes from baseline. These data will also be listed. The number and percentage of subjects with normal results, high/low results and abnormal clinical result (as judged by the PI) will be tabulated for laboratory parameters.

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.12	Summary of Clinical Chemistry Parameters – Safety Population
15.2.6.13	Summary of Hematology Parameters – Safety Population
15.2.6.14	Summary of Urinalysis Parameters – 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

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

12.6.4.5.1 Prior and Concomitant Medication

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

All medications will be listed by actual exposure using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organisation-Drug Dictionary Enhanced [WHO-DDE] Q1 2012). A flag will be presented on the listing indicating whether the medication is prior or concomitant. Partial dates will not be imputed, but assumptions will be made as follows to assign to either prior or concomitant:

Date information	Assign as
Missing stop date	Concomitant
Partial date, e.g. --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Screening.	Concomitant
Partial date, e.g. --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening.	Prior

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

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.10.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.10.2	Summary of Prior Medication by Preferred Drug Name – Safety Population
15.2.6.11.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.11.2	Summary of Concomitant Medication by Preferred Drug Name – Safety Population
LISTINGS	
15.3.6.3	Listing of Prior and Concomitant Medication

12.6.4.5.2 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -2) and at the day of Discharge (Day 6 or at the day of withdrawal for withdrawn subjects) will be listed by actual exposure. Subject's data with abnormal and abnormal clinically relevant physical examination findings will be flagged. The number and percent of subjects with normal, abnormal and abnormal clinically significant results will be tabulated by body systems at Screening, Admission and day of Discharge.

Body weight recorded at Admission and day of Discharge; and body height recorded at the Screening visit will also be listed together with BMI. Descriptive statistics of body weight, body height and BMI (BMI will also be categorized as shown in Section **7.5** "**Categorical Variables**"), at Admission and Day of Discharge will be presented.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.18	Summary of Weight and BMI Measurements – Safety Population
LISTINGS	
15.3.6.10	Listing of Physical Examination Findings, Shift and Changes from Baseline

12.6.4.5.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate values measured during the study will be listed by study visit, including low/normal/high results. Assessment after baseline (last assessment prior to 06:29 AM on Day 1) will include change from baseline.

Descriptive statistics will be presented for systolic and diastolic blood pressure, pulse rate and respiratory rate at baseline, and on every subsequent day of the confinement period by actual exposure for each study day. Vital signs data will be summarized together with changes from baseline.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

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

12.6.4.5.4 Spirometry

Spirometry parameters assessed during the study include:

- Measured forced expiratory volume in 1 second (FEV_1)
- Measured forced vital capacity (FVC)
- FEV_1/FVC
- Predicted FEV_1
- Percent of predicted FEV_1 (% 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, and Day of Discharge (Day 6 or day of withdrawal). At Screening, data are collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator.

Spirometry predicted values will not be standardized to the NHANES III predicted set as planned in the protocol. Predicted FEV_1 and FVC will be calculated according to the formula recommended by the Japanese Respiratory Society (**Sasaki H, Nakamura M et al., 2001**) for Japanese population.

Spirometry data values and normality evaluation will be listed by actual exposure and study day. Assessments performed after baseline (Day 0) will be listed together with change from baseline and shift in normality. Spirometry data from subjects who had relevant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for FEV_1(L), FEV_1 (% pred), FVC(L), FVC(% pred), and FEV_1/FVC at baseline, and Discharge by actual exposure, and overall. Spirometry data will be summarized together with changes from baseline (pre-bronchodilator), and the number and percentage of subjects with

normal/abnormal/abnormal clinically significant results. The post-bronchodilator data will not be included in these summaries, they will only be listed.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

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

12.6.4.5.5 Electrocardiogram

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

The baseline for the ECG data will be the Screening value.

ECG data values and normality evaluations will be listed by actual exposure and study day (Screening and Day 6) 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 by actual exposure. ECG data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.16	Summary of ECG Measurements – Safety Population
LISTINGS	
15.3.6.9	Listing of ECG Data and Changes from Baseline

12.6.4.5.6 Assessment of Cough

Cough questionnaire is assessed on a daily basis from Day 0 to Day 6. Questionnaire details are reported in Section **7.3.6** "**Cough Assessment**".

The number and % of subjects reporting a cough will be summarized by actual exposure. The responses to the individual items, including the VAS evaluating the level of cough bother and 3 Likert scales mesuring the intensity, the frequency of cough and the amount of sputum production will be listed and summarized on each day by study arm, for all subjects who filled in the questionnaire. The answers to the open question(s) related to any other important observation will be listed.

The data will be presented in the below outputs, the TFL number refers to the TFL number in the accompanying TFL shell document:

TFL number	Title
TABLES	
15.2.6.19	Summary of Cough Assessments Over Study – Safety Population
15.2.6.19.1	Summary of Cough Assessments by Study Day – Safety Population
LISTINGS	
15.3.6.14	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 [redacted] will be responsible for the monitoring of the study. Monitoring will be performed according to [redacted] standard operating procedures (SOPs) and as per the agreed monitoring plan with PMI.

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

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

13.2 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 no.	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
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – FAS

TFL no.	Title
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS
15.2.2.1	Summary of Use of THS 2.2 Product and CC – Safety Population
15.2.6.1	Summary of Adverse Events – Safety Population
15.2.6.2.1	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.3	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.4	Summary of Adverse Events Leading to Study Product Discontinuation or Reduction by System Organ Class and Preferred Term – Safety Population
15.2.6.5	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.6	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population
15.2.6.7	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.8	Summary of Serious Adverse Events – Safety Population
15.2.6.9	Summary of THS 2.2 Device Events – Safety Population
15.2.6.9	Summary of THS 2.2 Device Events – Safety Population

13.3 Topline Results

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

TFL no.	Title
FIGURES	
15.1.1.1	Blood COHb (%) Mean and 95% CI– FAS
15.1.1.2	MHBMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.1.3	3-HPMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
15.1.1.4	S-PMA Urinary Concentration Adjusted for Creatinine Mean and 95% CI– FAS
TABLES	
15.2.3.1	Analysis of Blood COHb (%) versus CC on Day 5 – FAS
15.2.3.2	Analysis of MHBMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – FAS
15.2.3.3	Analysis of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – FAS

TFL no.	Title
15.2.3.4	Analysis of S-PMA Urinary Concentration Adjusted for Creatinine (units) versus CC on Day 5 – FAS
15.2.3.5	Descriptive Statistics of % Change in Primary Biomarkers of Exposure on Day 5 – FAS
15.2.3.5.1	Descriptive Statistics of % Change in Primary Biomarkers of Exposure on Day 5 by Sex – FAS
15.2.3.5.2	Descriptive Statistics of % Change in Primary Biomarkers of Exposure on Day 5 by Cigarette Consumption – FAS
15.2.3.6	Descriptive Statistics of Blood COHb (%) – FAS
15.2.3.6.1	Descriptive Statistics of Blood COHb (%) by Sex – FAS
15.2.3.6.2	Descriptive Statistics of Blood COHb (%) by Cigarette Consumption – FAS
15.2.3.7	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) – FAS
15.2.3.7.1	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS
15.2.3.7.2	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS
15.2.3.8	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) – FAS
15.2.3.8.1	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS
15.2.3.8.2	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS
15.2.3.9	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) – FAS
15.2.3.9.1	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Sex – FAS
15.2.3.9.2	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (units) by Cigarette Consumption – FAS
15.2.4.5	Analysis of Primary Biomarkers of Exposure versus SA – FAS
15.2.4.6	Analysis of Urinary Quantity Excreted of MHBMA, 3-HPMA and SPMA over 24 hours – FAS
15.2.4.7	Descriptive Statistics of Urinary Quantity Excreted of MHBMA over 24 hours (units) – FAS
15.2.4.8	Descriptive Statistics of Urinary Quantity Excreted of 3-HPMA over 24 hours (units) – FAS
15.2.4.9	Descriptive Statistics of Urinary Quantity Excreted of SPMA over 24 hours (units) – FAS
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – FAS

TFL no.	Title
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – FAS
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption – FAS
15.2.6.1	Summary of Adverse Events – Safety Population
15.2.6.2.1	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.6.2.2	Summary of Adverse Events by System Organ Class – Safety Population
15.2.6.2.3	Summary of Adverse Events by Preferred Term – Safety Population
15.2.6.3	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness – Safety Population
15.2.6.4	Summary of Adverse Events Leading to Study Product Discontinuation or Reduction by System Organ Class and Preferred Term – Safety Population
15.2.6.5	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.6	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term – Safety Population
15.2.6.7	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.8	Summary of Serious Adverse Events – Safety Population

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 no.	Title
TABLES	
15.2.3.1	Analysis of Primary Biomarkers of Exposure versus CC – FAS
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									Safety Follow-Up[o]
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-14**
Informed consent for study participation and two informed consents for bio-banking	●										
Admission/Discharge		●								●	
Advice on the risk of smoking and debriefing	●	●								●	
Support for SA arm					●	●	●	●	●		
Inclusion/exclusion criteria	●	●									
Enrollment		●									
Randomization				●							
Demographics, medical history, concomitant diseases	●										
Vital signs [a]	●	●	●	●	●	●	●	●	●	●	
Physical examination [b]	●	●								●	
Spirometry [c]	●			●						●	
Prior/concomitant medication	●	●	●	●	●	●	●	●	●	●	●
B/U: Hematology, clinical chemistry, urine analysis	●			●						●	
Electrocardiogram	●									●	
Chest X-ray [d]	●										
B: HIV, hepatitis B and C	●										
U: Urine drug screen, urine cotinine screening	●	●									

	Screening	Confinement Period									Safety Follow-Up[o]
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-14**
test											
U: Pregnancy test	●	●								●	
Alcohol breath test	●	●									
FTND	●										
Smoking history	●	●									
Willingness to quit smoking [e]	●	●									
Identification of cigarette brand	●	●									
THS 2.2 demonstration	●										
THS 2.2 product test [f]		●									
CO breath test [g]		●	●	●	●	●	●	●	●	●	
B: BoExp in blood: COHb [h]			●	●	●	●	●	●	● (x4)		
B: Biomarker of exposure in plasma: nicotine, cotinine [i]				●	●	●	●	●	●	●	
B: CYP1A2 activity				●					●		
B: CYP2A6 activity				●						●	
QSU-brief questionnaire [j]			●	●	●	●	●	●	●		
MNWS (revised version) [k]				●	●	●	●	●	●	●	
MCEQ (modified version; THS 2.2 and CC arms) [l]			●	●	●	●	●	●	●		
HST (THS 2.2 and CC arms) [m]				●	●			●			
HST questionnaire (THS 2.2 and CC arms)				●				●			
Assessment of cough				●	●	●	●	●	●	●	
AE/SAE recording	●	●	●	●	●	●	●	●	●	●	●
Collection tobacco plugs of used Tobacco Sticks					●	●	●	●	●		

	Screening	Confinement Period									Safety Follow-Up[o]
Study Day	**-30 to -3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-14**
for combustion analysis and accountability											
Collection of used CC butts for accountability			●	●	●	●	●	●	●		
B: Bio-banking for BoExp and risk markers [n]				●						●	
B: Bio-banking for transcriptomics[n]				●						●	

Abbreviations: AE = adverse event; B = blood sample required; CC = conventional cigarette(s); CO = carbon monoxide; CoHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; FTND = Fagerström Test for Nicotine Dependence; HIV = human immunodeficiency virus; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence; SAE = serious adverse event; THS = tobacco heating system; U = urine sample required.

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

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

c: Spirometry does not need to be done prior to smoking at screening. At screening, spirometry without brochondilator will be done first and then with. On Day 0 and Day 6, spirometry has to be done prior to smoking.

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

e: Subjects will be asked if they plan to quit smoking within the next 3 months (at Screening only) and, in order to satisfy the protocol inclusion criteria, if they are ready to abstain from smoking for at least 5 days (at Screening and Day -2).

f: THS 2.2 product test to be conducted as the last procedure of eligibility check at Day -2 (and after urine pregnancy test has been done in female subjects to exclude pregnancy).

g: 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 THS 2.2 and CC arms) and between 08:00 AM and 09:30 AM for subjects in the SA arm. The other three tests should be conducted between 12:00 PM and 01:30 PM, 04:00 PM and 05:30 PM, and 08:00 PM and 9:30 PM. Day -2 and Day 6: once during the visit, irrespective of the time of product use.

h: 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 and 09:30 PM.
Day 5: one blood sample within 15 minutes prior to the first product use (for subjects in the THS 2.2 and CC arms) and between 08:00 AM and 9:30 AM for subjects in the SA arm, and one blood sample between 12:00 PM and 01:30 PM, 04:00 PM and 05:30 PM, and 08:00 PM and 9:30 PM.

i: Nicotine/cotinine; Day 0 to Day 4 (all study arms): one blood sample in the evening between 08:00 PM and 09:30 PM.
Day 5 and Day 6 (THS 2.2 and CC arms): one sample within 15 minutes prior to the first product use (T0); eight blood samples afterT0 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 and 09:30 PM. On Day 6, one blood sample to be drawn in the morning between 08:00 AM and 9:30 AM.

j: QSU-brief: Daily, from Day -1 to Day 5.

k: MNWS: daily from Day 0 to Day 6.

l: MCEQ: Day -1 to Day 5 on a daily basis. On Day -1 and Day 0, all subjects will complete the questionnaire. From, Day 1, only subjects who are randomized to the THS 2.2 and CC arms will complete this questionnaire.

m: On Day 0, HST and HST questionnaire will be done in all subjects smoking CC compatible with the HST SODIM® device. On Day 1 and Day 4, HST and HST questionnaire will be done in all subjects in the THS 2.2 and CC arms.

Smoking topography with the HST device will not be done in subjects smoking CC that are incompatible with the HST SODIM® device (e.g. slim CC). No HST assessments will be done in subjects in the SA arm.
n: Samples will only be taken if additional consent for BoExp bio-banking is given by the subject.
o: all safety examinations listed on the Day of Discharge (Day 6) will be conducted in subjects whose participation in the study is prematurely terminated.

Table A2 Schedule for 24-hour Urine Collection Assessments

	Baseline period		Confinement Exposure Period				
24 hour urine samples	**Day -1 to Day 0**	**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**
BoExp in urine [a]	●	●	●	●	●	●	●
Creatinine	●	●	●	●	●	●	●
Ames mutagenicity test, 11-DTX-B2 and 8-epi-PGF2α		●					●
Bio-banking [b]		●					●

Abbreviations: 8-epi-PGF2α = 8-epi-prostaglandine F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2
a: BoExp in urine: Primary (MHBMA, 3-HPMA, S-PMA); Secondary (total NNAL, 1-NA, 1-OHP, total NNN, 3-hydroxy(a)benzopyrene, 4-ABP, 2-NA, o-tol, Neq, CEMA, HEMA, S-BMA and HMPMA). In the above table, the dot corresponds to the day on which the 24-hour urine collection period starts. The end of the 24-hour urine collection period will be the following day.
b: Samples will only be taken if additional consent for BoExp bio-banking is given by the subject.