STATISTICAL ANALYSIS PLAN

A single-centre, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine gum

Study Product: Tobacco Heating System 2.2

Sponsor Reference No.: ZRHR-PK-02-JP
CDARO No.: 1001000-8278002

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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).

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3 INTRODUCTION

This SAP has been developed to supplement the statistical analyses described in the clinical study protocol final version 1.0 dated 21 June 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 TFL shells 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**).
- The Committee for Medicinal Products for Human Use (CHMP) Guideline on the Investigation of Bioequivalence (**CHMP, 2010**).
- The Appendix IV of the CHMP Guideline on the Investigation on Bioequivalence (**CHMP Appendix IV, 2011**).
- Food and Drug Administration (FDA) Guidance to Industry for Statistical Approaches to Establishing Bioequivalence (**FDA, 2001**).
- Electronic case report forms (eCRF) Version 2.0 dated 20 September 2013.
- Biostatistical Addendum – Subject Randomization List version 2.0 (16 April 2013).

3.1 Revision History

Version	Date of Revision	Revision
2.0	07 April 2014	• Due to the large number of T_0 nicotine concentrations that were higher than expected, the following changes to the statistical analyses were made: 1) The primary analysis was changed to include all subjects irrespective of their T_0 concentrations (with respect to their C_{max}). 2) The originally planned analysis (SAP v 1.0) became a supportive analysis. • A typo in the formula for CYP2A6 activity was corrected
1.0	02 October 2013	Original SAP

4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used within this SAP.

$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from t_{last} to infinity
AE/SAE	Adverse Event/ Serious Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic and Chemical
AUC	Area under the curve
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from start of product use extrapolated to infinite time
$AUC_{(0-last)}$	Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration.
$AUC_{(0-t')}$	Area under the plasma concentration-time curve from start of product use to the subject-specific t'
AUQ	Above the Upper limit of Quantification
BLQ	Below the Lower limit of Quantification
BMI	Body Mass Index
CC	Conventional Cigarettes
CH	Cigarette Holder
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{last}	The last quantifiable concentration
C_{max}	Maximum observed plasma concentration.
CO	Carbon Monoxide
COHb	Carboxyhemoglobin
COT	Cotinine
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CV	Coefficient of Variation
CYP2A6	Cytochrome P450 2A6
DDE	Drug Dictionary Enhanced
ECG	Electrocardiogram
eCRF	Electronic case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced Vital Capacity
HCOT	Trans-3'hydroxycotine
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

ISO	International Organization for Standardization
IXRS	Interactive Voice and Web Response System
LLOQ	Lower Limit of Quantification
LS	Least Squares
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MSE	Mean square error of the fitted model residual
NR	No Result
NRT gum	Nicotine Replacement Therapy gum
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred Term
QC	Quality Control
QSU-brief	Questionnaire of Smoking Urges Brief
QTcB	QT Interval Corrected using Bazett's Formula
QTcF	QT Interval Corrected using Fridericia's Formula
RBC	Red blood cells
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
t'	The subject-specific time of maximum nicotine concentration following single use of the CC or NRT gum product, between the THS 2.2 and CC, as well as the THS 2.2 and NRT gum
T_0	Time of first product use at single use day
$t_{½}$	Terminal elimination half-life
TFL	Tables, Figures, and Listings
THS	Tobacco Heating System
t_{last}	Time of last quantifiable concentration
t_{max}	Time of maximum observed plasma concentration
ULOQ	Upper Limit of Quantification
VAS	Visual Analogue Scale
WBC	White blood cells
WHO	World Health Organisation
λ_z	Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data

The following special terms are used in this SAP:

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.
Enrolment	On Day -1 for eligible subjects (all applicable inclusion and exclusion criteria have been satisfactorily met) and the subjects is willing and ready to use both the THS 2.2 and NRT gum (the test of both THS 2.2 and NRT gum are the last assessments prior to enrolment)
First product use within each Single Use day	Start of product use: • THS 2.2 is defined as the time of the first puff. • CC corresponds to the lighting of the CC • NRT gum is the time of NRT gum intake
Randomization	Assignment to product on Day 0 using an IXRS
Safety follow-up	After the 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. In general any AE will be followed up until resolved, stabilized i.e. no worsening of the event or a plausible explanation for the event has been found.
Screening failure	Subjects who do not enroll in to the study
Back up subjects	Subjects who tested the product but were not enrolled or were discontinued from enrollment
Tobacco Heating System 2.2 (THS 2.2)	THS 2.2 is composed of the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.

5 STUDY OBJECTIVES AND ENDPOINTS

The endpoints specify randomization groups (Group-1 or Group-2) that are being analyzed for the objective when it is not applied to both (the randomization groups are defined in Table 1 of Section 6.1).

5.1 Primary Objective and Endpoints

1. To evaluate the rate and the amount of nicotine absorbed (as assessed by maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC] from start of product use to time of last quantifiable concentration [$AUC_{(0\text{-last})}$]) from THS 2.2 relative to conventional cigarettes (CC), following single use of THS 2.2 and CC.

   Endpoints:
   - C_{max} [CC and THS 2.2, Group-1]
   - $AUC_{(0\text{-last})}$ [CC and THS 2.2, Group-1]

5.2 Secondary Objectives and Endpoints

1. To determine if C_{max} and $AUC_{(0\text{-last})}$ of plasma nicotine of the THS 2.2 are higher relative to Nicotine Replacement Therapy gum (NRT gum) following single use of the THS 2.2 and NRT gum.

   Endpoints:
   - C_{max} [NRT gum and THS 2.2, Group-2]
   - $AUC_{(0\text{-last})}$ [NRT gum and THS 2.2, Group-2]

2. To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to time of last quantifiable concentration to infinity [$AUC_{(0\text{-}\infty)}$] and partial AUC, where t' is the subject-specific time of maximum nicotine concentration following single use of the CC or NRT gum [$AUC_{(0\text{-}t')}$]) between the THS 2.2 and CC, as well as the THS 2.2 and NRT gum.

   Endpoints:
   - $AUC_{(0\text{-}\infty)}$.
   - Partial $AUC_{(0\text{-}t')}$.

3. To evaluate the time to the maximum concentration (t_{max}) of plasma nicotine for the THS 2.2 as compared to CC and to determine if the t_{max} for THS 2.2 is shorter as compared to NRT gum.

   Endpoint:
   - t_{max}.

4. To describe the terminal half-life ($t_{1/2}$) of nicotine for the THS 2.2, CC, and NRT gum.

Endpoint:

- $t_{½}$.

5. To describe the differences on urge-to-smoke over time between the THS 2.2 and CC, as well as between the THS 2.2 and NRT gum.

   Endpoints:

   Urge-to-smoke as measured with the Questionnaire of Smoking Urges brief (QSU-brief) (**Cox et al, 2001**).

   - Total score.
   - Factor-1.
   - Factor-2.

6. To describe product evaluation in the THS 2.2 and CC users.

   Endpoints:

   Product evaluation as measure with the Modified Cigarette Evaluation Questionnaire (MCEQ) (**Cappelleri et al, 2007**) [CC and THS 2.2, in Group-1]

   - Smoking Satisfaction subscale.
   - Enjoyment of Respiratory Tract Sensation subscale.
   - Psychological Reward subscale.
   - Aversion subscale.
   - Craving Reduction subscale.

7. To describe the levels of carbon monoxide (CO) exposure for the THS 2.2, as compared to CC and NRT gum users.

   Endpoints:

   - Levels of exhaled CO.
   - Carboxyhemoglobin (COHb) in blood.

8. To monitor the safety 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 and Likert scales and one open question.
   - Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate).
   - Spirometry.
   - Electrocardiogram (ECG).
   - Clinical chemistry, hematology, and urine analysis safety panel.
   - Physical examination.

- Concomitant medication.

5.3 Additional Endpoints

The following additional 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**).
- Cytochrome P450 2A6 (CYP2A6) activity (nicotine metabolic molar ratio) in plasma.

5.4 Study Hypotheses And Evaluation Criteria

5.4.1 Hypotheses

Given that the primary objective of this study is to determine the point estimate and precision of the nicotine relative bioavailability (ratio of THS 2.2:CC) for C_{max} and $AUC_{(0\text{-last})}$, there is no statistical hypothesis to be tested for the primary objective.

For the secondary objectives the following hypotheses will be examined for THS 2.2 versus NRT gum analysis:

The hypotheses to be tested for the secondary objectives are:

- The geometric mean C_{max} in THS 2.2 is higher relative to NRT gum.
- The $AUC_{(0\text{-last})}$ in THS 2.2 is larger relative to NRT gum.
- The median t_{max} in THS 2.2 is shorter than in NRT gum.

5.4.2 Evaluation Criteria

The study will be considered successful if the 95% confidence intervals (CI) of the THS 2.2:CC ratio for the nicotine C_{max} and $AUC_{(0\text{-last})}$ are estimated with a precision of ±20%.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a randomized, controlled, 2-period, 4-sequence, single-use crossover study. An incomplete block design has been adopted, where each subject will receive only two of the three products (Figure 1):

- THS 2.2
- CC

- NRT gum

In total, 62 eligible, healthy smoking subjects will be randomized into one of the 4 sequences in Table 1:

Table 1 Definition of Randomization Groups and Sequences

Group	Allocation Ratio	Sequence	Sample Size
Group-1 = THS 2.2 vs. CC	2:2	1. THS 2.2 then CC	22
		2. CC then THS 2.2	22
Group-2 = THS 2.2 vs. NRT gum	1:1	3. THS 2.2 then NRT gum	9
		4. NRT gum then THS 2.2	9

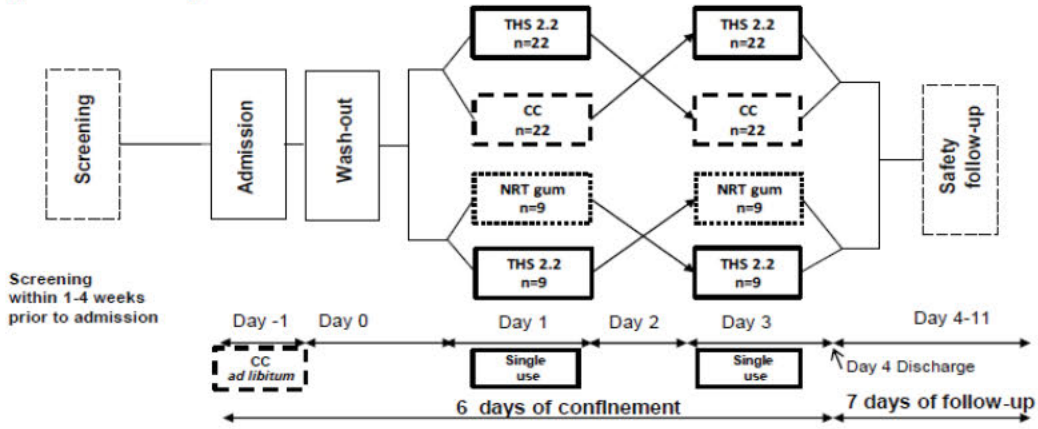
A Screening Visit will be conducted within 4 weeks prior to Admission to the investigational site (Day -29 to Day -2). A demonstration of the THS 2.2 product and the NRT gum will also be done by the site study collaborator during the screening visit. Subjects will be admitted to the clinic on Day -1 (Admission). On Day -1, as the last procedure of the eligibility assessments on that day, all subjects will undergo a product test prior to enrolment, first THS 2.2 (using of up to 3 Tobacco Sticks) and subsequently NRT gum. In female subjects, the urine pregnancy test must be negative before any product test is performed with either the THS 2.2 or the NRT gum. After all inclusion and exclusion criteria have been satisfactorily met, only subjects willing and ready to use both the THS 2.2 and the NRT gum products can be enrolled. Screening procedures do not necessarily have to be conducted on the same day.

Subjects are enrolled on Day -1, but not randomized until the Day 0 washout, therefore it is possible to have enrolled subjects who do not get randomized.

Subjects will be discharged from the investigational site in the morning of Day 4 after all safety examinations of the Day of Discharge have been conducted. 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 confinement period consists of 2 periods (Period 1, Period 2) with each period consisting of at least 24-hour nicotine wash-out (nicotine abstinence) and 1 day of single product use.

Figure 1. Study Flowchart



Abbreviations: THS: Tobacco Heating System; CC = conventional cigarette; NRT = Nicotine Replacement Therapy

6.1.1 Timing of Confinement Period

The 6 day confinement period consists of:

- The Admission Day from admission on site until 06:30 AM on Day 0.
- The first washout period: from 06:30 AM on Day 0 until the time of first product use (T_0) in the time window 6:00 AM-9:00 AM of Day 1.
- The first product exposure period (1 day): starting from T_0 on Day 1, ending 24 hours after T_0.
- The second washout period: from the end of the first product exposure (24 hours after T_0 on Day 1) on Day 2 until the time of product use in the time window 6:00 AM-9:00 AM on Day 3.
- The second product exposure period (1 day): starting from T_0 on Day 3, ending 24 hours after T_0.
- The discharge procedures from 24 hours after T_0 of the second product use until the time of discharge on Day 4.

6.2 Selection of Study Population

6.2.1 Inclusion Criteria

A total of 62 smoking, healthy adult Japanese subjects, meeting the following inclusion criteria will be randomized on to the 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 Principal Investigator (PI) based on all available assessments in the Screening period / day of admission.

5. Subject smokes at least 10 commercially available CC per day (no brand restrictions) for the last 4 weeks, based on self-reporting and has been smoking for at least the last 3 consecutive years.
6. Subject does not plan to quit smoking in the next 3 months.
7. The subject is ready to accept interruptions to smoking for up to 4 days.
8. The subject is ready to accept using the THS 2.2 and the NRT gum product.

6.2.2 Exclusion Criteria

The exclusion criteria are:

1. As per PI judgement, 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 judgement of the PI.
4. The subject has a body mass index (BMI) <18.5 or ≥ 32.0 kg/m^2.
5. 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 (prescription or over the counter) within 14 days or within 5 half-lives of the drug prior to the Admission Day that has an impact on CYP2A6 activity.
8. In case the subject received any medication (prescribed or over the counter) within 14 days prior to Screening or prior to the Admission Day (Day -1) it will be decided at the discretion of the PI if these can potentially interfere with the study objectives and subject's safety.
9. 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.
10. The subject has a positive urine drug test.
11. Positive serology test for HIV 1/2, Hepatitis B or Hepatitis C.
12. Donation or receipt of whole blood or blood products within 3 months prior to Admission.
13. The subject is a former or current employee of the tobacco industry or of their first-degree relatives (parent, sibling or child).
14. 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).
15. The subject has participated in a clinical study within 3 months prior to the Screening Visit.
16. 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).
17. For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding.

18. For women only: Subject does not agree to use an acceptable method of effective contraception.*

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

6.3 Product Allocation and Blinding

6.3.1 Methods of Assigning Subjects to Treatment Sequences

Randomization will be conducted through the Interactive Web and Voice Response System (IXRS).

Subjects will be randomized to either Group-1 (sequence 1 and 2) or to Group-2 (sequence 3 and 4). Each stratum: sex (male and female) and CC nicotine level at Admission (International Organization for Standardization [ISO] nicotine level ≤0.6 mg and >0.6≤1 mg) will have a quota applied to ensure they represent at least 40% of the total study population. See Table 1.

To accomplish the above, the subject randomization list will contain randomization records for the 2 groups. A blocked randomization will be used. Subjects will be assigned to the next available sequence providing the quotas have not been met. Block size and other randomization details are available in the randomization plan.

The randomization scheme will be generated by the statistical division within (b)(4) and none of the study team, including study sponsor, (b) (4), and PI or the 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 PI will be unblinded to subject's sequence and product assignment after randomization. However, there will be a limited degree of blinding during the conduct of the study including the data review and data analysis process. In particular, PMI and (b) (4) personnel will be blinded to the randomized sequence as summarized in Table 2.

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[2].
PMI safety and clinical scientist	After the finalization of PMI blind database review[2]. Can be actively un-blinded before that time point in case of the occurrence of any safety question, when appropriate.

[1] A [redacted] PK expert will perform an unblinded data review of PK data and will flag any anomalous data for the pre-analysis blinded data review conducted by PMI and [redacted].

[2] As part of the PMI Quality Control (QC) activity, data listings will be reviewed by Covance and PMI before database lock, with no access to the randomization sequence 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.

No unblinding information will be shared with the blinded study team without a dummy randomization or masking in place, until the end of the blinding period (see Table 2). 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 will be ensured by strict distribution of the products (product by product) and collection of used Tobacco Sticks, the CC butts and the NRT gum after use. This information will be documented in appropriate logs.

In addition, in subjects using NRT gum, the compliance will be chemically verified using exhaled CO breath. The cut-off point for the CO breath test value to distinguish tobacco use vs. no tobacco use will be 10 ppm (**Bennowitz et al, 2002**).

Furthermore, the CO breath test will be considered as a measure of compliance during the wash-out days for all subjects.

7 DERIVED AND COMPUTED VARIABLES

Mean change from baseline is the mean of all individual subjects' change from baseline values (baseline is defined in Section 11.1.4 "Definitions for Statistical Data Analysis"). 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.

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

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

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

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

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

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

The geometric coefficient of variation (CV) will be calculated using the following formula:

$$CV = 100\sqrt{e^{var} - 1}$$

where var = the variance from the log transformed data.

7.1 Pharmacokinetic Parameters

The following PK parameters will be determined from the plasma concentration-time profiles of nicotine using non-compartmental procedures in WinNonlin Phoenix, Version 6.2.1, or higher:

Table 3: Definition of PK Parameters

Parameter	Definition
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration.
$AUC_{(0\text{-t'})}$	Area under the plasma concentration-time curve from start of product use to the subject-specific time (t') of maximum nicotine concentration following single use of the CC or NRT gum product, between the THS 2.2 and CC, as well as the THS 2.2 and NRT gum.
$AUC_{(0\text{-}\infty)}$	Area under the plasma concentration-time curve from start of product use extrapolated to infinite time.
$\%AUC_{extrap}$	Percentage of AUC that is extrapolated from t_{last} to infinity.
C_{max}	Maximum observed plasma concentration.
C_{last}	Last quantifiable concentration.
t_{last}	Time of the last quantifiable concentration.
t_{max}	Time of maximum observed plasma concentration.
λ_z	Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data.
$t_{1/2}$	Terminal elimination half-life.

Additional PK parameters may be determined in order to support the interpretation where appropriate.

The actual blood sampling times post-exposure collected in the eCRF will be used in the computation of the PK parameters, with the exception of pre-exposure (-15 mins) blood sampling time which will be considered as time zero (T_0).

7.1.1 Calculation of C_{max} and t_{max}

The minimum requirement for the determination of the C_{max} is the inclusion of at least one quantifiable concentration within 1 hour post-exposure.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of the C_{max}.

7.1.2 Calculation of AUC

The minimum requirement for the calculation of the AUC is the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

$AUC_{(0\text{-last})}$ and $AUC_{(0\text{-t'})}$ will be calculated using the linear trapezoidal method.

$AUC_{(0\text{-t'})}$ will be calculated automatically by linear interpolation within WinNonlin, where t' is the subject-specific actual time of maximum nicotine concentration following single

use of the CC or NRT gum product, between the THS 2.2 and CC, as well as the THS 2.2 and NRT gum.

$AUC_{(0-\infty)}$ will be calculated as follows:

$$AUC_{0-\infty} = AUC_{0-last} + \left(\frac{C_{last}}{\lambda_z} \right)$$

Where C_{last} is the last quantifiable concentration and λ_z is the terminal elimination rate constant.

$\%AUC_{extrap}$, the percentage of $AUC_{(0-\infty)}$ extrapolated beyond t_{last}, will be calculated according to the following formula:

$$\%AUC_{extrap} = \left(1 - \frac{AUC_{0-last}}{AUC_{0-\infty}} \right) \text{x } 100$$

$AUC_{(0-\infty)}$ values where the percentage extrapolation is greater than 20% will be flagged in the data listings and will be reviewed for inclusion in the analysis during the ore-analysis data review.

7.1.3 Criteria for Calculating the Apparent Terminal Elimination Half-Life

$t_{1/2}$ will be calculated according to the following formula:

$$t_{½} = \frac{\ln(2)}{\lambda_z}$$

where λ_z will be calculated by least squares (LS) linear regression of the terminal portion of the log-transformed plasma concentration-time curve.

The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. The concentrations included in the terminal elimination phase will be flagged in the data listings.

Period of Estimation

- Apparent terminal (elimination) half-lives will be calculated, where possible, over at least 2 half-lives. Where an apparent terminal half-life is estimated over less than 2 half-lives, it will be flagged in the data listings.

- An apparent terminal half-life will not be reported if it can only be calculated over a period that is less than 1.5 half-lives.

Number of Data Points

- At least 3 data points with nicotine concentration greater than the LLOQ will be used for each subject in the regression analysis. An apparent terminal half-life will not be reported if derived from less than 3 data points.

Goodness of Fit

- When assessing apparent terminal phases, the coefficient of determination, R^2 adjusted value, will be used as a measure of the goodness of fit of the data points to the determined line. This parameter will be used as it is considered to be a better assessment of the goodness of fit, compared to R^2, as it adjusts for the number of points included in the line therefore allowing for a more direct comparison between elimination phases determined using different numbers of data points.
- Apparent terminal half-life will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

7.1.4 Anomalous Values

If a concentration value is considered to be anomalous due to being inconsistent with the expected PK profile it will be flagged in the listings and will be reviewed for inclusion in the analysis during the pre-analysis data review.

7.2 Biomarkers

7.2.1 CYP2A6

CYP2A6 activity is calculated in plasma as the metabolic ratio of trans-3' hydroxycotinine and cotinine, both expressed in molar equivalent (nmol/L) (**Jacob et al, 2011**):

$$CYP2A6 = \frac{HCOT[ng/mL] \times 5.202}{COT[ng/mL] \times 5.675}.$$

Any values below the LLOQ or above the upper limit of quantification (ULOQ) in the component parameters will not be imputed and the derived variable will be set to missing.

The conversion factor will be applied as follows:

Cotinine (COT)	The molecular weight is 176.2178 g/mol (**Chemical Information Specialized Information Services RN:486-56-6**) Therefore to transform COT from ng/mL to nmol/L, the result in ng/mL will be multiplied by 5.675

Trans-3'hydroxycotine (HCOT)	The molecular weight is 192.217 g/mol (**Chemical Information Specialized Information Services RN:34834-67-8**) Therefore to transform HCOT from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202

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

7.3 Questionnaires

7.3.1 Fagerström Test for Nicotine Dependence

The FTND will be used in its revised version (**Heatherton et al, 1991**). These questions are to be answered by the subject themselves. It is conducted at Screening only to determine subject's dependence on nicotine.

Table 4 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 4: 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
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

The QSU-brief (**Cox et al, 2001**). is a self-reported questionnaire completed 10 times at the following timepoints at Day 1 and Day 3:

- The first assessment will be done 15 min prior to T_0
- The subsequent 9 assessments will be done as follows:
  - For subjects on THS 2.2 or CC, assessments will be done at: T_0+15 min, T_0+30 min, T_0+45 min, T_0+1 hr, T_0+2 hr, T_0+4 hr, T_0+6 hr, T_0+9 hr, T_0+12 hr (with an allowed time window of +10 min each).
  - For subjects on NRT gum, assessments will be done at: T_0+20 min, T_0+30 min, T_0+45 min, T_0+1 hr, T_0+2 hr, T_0+4 hr, T_0+6 hr, T_0+9 hr, T_0+12 hr (with an allowed time window of +10 min each).

The QSU-brief consists of 10 items as presented in Table 5.

Table 5: 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 be derived (**Cox et al, 2001**). Each factor is a subset that includes 5 of the 10 questions as defined in Table 5. 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 at Day 1 and Day 3, during CC and THS 2.2 (product use only) to assess the degree to which subjects experience the reinforcing effects of smoking.

The MCEQ consists of 12 items as presented in Table 6.

Table 6: 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 Cough Assessment

Subjects will be asked if they have experienced a regular need to cough (e.g., coughing several times) in the last 24 hours prior to assessment. If the answer is 'yes', they will be asked to complete a visual analogue scale (VAS), three Likert scale questions and an open question assessing their cough during previous 24 hours. Assessments will be done on a daily basis from Day 0 to Day 4.

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.

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 Categorical Variables

Table 8: Categorical Variable 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
ISO nicotine level (mg)	≤ 0.6	
	> 0.6 to ≤ 1.0	
	> 1.0[1]	
ISO tar yields (mg)	1-5	
	6-8	
	9-10	
	>10[1]	
Daily CC consumption (cig/day)	<10[1]	
	10-19	
	>19	
NRT Use	< 10 min	
	≥10 min and <30 min	
	35±5 min	
	>40 min	
CO breath test level (ppm)	≤ 10	
	> 10	

Table 8: Categorical Variable Definitions

Variable	Categories
COHb level	≤ 2% > 2%
Adverse event severity	Mild Moderate Severe
Adverse event relationship	Related Not related
Adverse event expectedness	No Yes
Action taken due to adverse event	Discontinuation from study Related to product use (if any of the following applies: interrupted, stopped, or reduced) Treatment given (yes/no) Other action taken
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, or with ISO nicotine level > 1.0 mg, or ISO tar yields > 10mg; therefore these categories will not be presented unless there is at least one response.

8 SAMPLE SIZE JUSTIFICATION

A total of 62 subjects will be randomized. This sample size is the sum of the sample size requirements for the THS 2.2:CC comparison and the THS 2.2:NRT gum comparison (as described in detail below).

The estimates for the within-subject CV for nicotine C_{max} (36%) and $AUC_{(0\text{-last})}$ (21%) are based on the data collected in the ZRHX-PK-02 clinical study (**ZRHX-PK-02, 2012**) comparing the nicotine PK profiles of Tobacco Heating System 2.1, the predecessor of THS 2.2 (regular tobacco stick) and CC. In the absence of data comparing THS and NRT gum, the same CVs were assumed for the calculation of the sample size related to the THS 2.2:NRT gum comparison.

Anticipated mean C_{max} and $AUC_{(0\text{-last})}$ for THS 2.2 and CC were based on data from the ZRHX-PK-02 study (**ZRHX-PK-02, 2012**). Anticipated mean C_{max} and $AUC_{(0\text{-last})}$ for NRT gum were based on data reported by **Dautzenberg et al., 2007**.

The sample sizes of this study assume a drop-out rate no larger than 10%.

Sample size calculations were conducted using SAS® version 9.2 for the 95% CI of the mean differences between paired observations (proc power onesamplemeans) in the natural log scale (**Senn, 2002**). The SAS® implementation of the method published by **Beal, 1989** was adopted to estimate the probability of obtaining at most the target 95% CI of ±20%.

A total of 44 subjects are needed to estimate the geometrical mean C_{max} ratio between THS 2.2 and CC with a 90% probability of obtaining a margin of error (95% CI) of at most ±20%, assuming that THS 2.2 have a nicotine C_{max} similar to CC (geometrical mean ratio equal to 1.00). This sample size is sufficient to provide 90% probability of obtaining a margin of error of at most ±20% for the geometrical mean $AUC_{(0\text{-last})}$ ratio between THS 2.2 and CC, assuming a similar extent of nicotine absorption for the 2 products (ratio equal to 1.00).

A total of 18 subjects are needed to estimate the geometrical mean $AUC_{(0\text{-last})}$ ratio between THS 2.2 and NRT gum with a precision allowing for the lower bound of the 95% CI exceeding 1.00, with 90% power, assuming a ratio of 1.28 between the geometrical mean of THS 2.2 and NRT gum. This sample size is sufficient to provide 90% power of obtaining a lower bound of the 95% CI of the geometrical mean C_{max} ratio between THS 2.2 and NRT gum, exceeding 1.00, assuming a geometrical mean ratio between THS 2.2 and NRT gum of 2.00.

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

Safety analyses will not be performed by product. Due to the study design it was determined that this presentation is not clear because of the product test at Admission and the selection of arbitrary time points for defining periods associated to the different study products may be misleading. In addition, the safety laboratory evaluations will only be collected prior to any product use and following the use of both products.

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

Statistical analysis for blood COHb (%) and exhaled CO (ppm) measurements and the QSU-brief questionnaire data will be performed including interaction terms for product and time point to enable LS 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.

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.

10 ANALYSIS POPULATIONS

For analysis purposes, actual product exposure during single use days will be defined as:

- THS 2.2: if there is a non-missing time for "Time of First Puff" (from THS 2.2 consumption page in eCRF), and no other product exposure definition is applicable.
- NRT gum: if there is a non-missing "Time of first NRT gum intake" and "Time of last chew " (from the NRT gum consumption page in eCRF), and no other product exposure definition is applicable.
- CC: if there is a non-missing "Time of lighting the CC" (from CC product consumption eCRF page), and no other product exposure definition is applicable.

All endpoints (other than safety) will be analyzed using the PK populations. Safety will be analyzed using the safety population.

10.1 PK Populations

The analysis populations for the PK endpoints are composed of two populations to allow the comparison between THS 2.2 and NRT gum (Group-1 PK) separately from the comparison between THS 2.2 and CC (Group-2 PK).

The PK populations consist of all the randomized subjects who give informed consent, completed at least one of the single use days (Day 1 or Day 3), and for whom at least one PK parameter can be derived. Only subjects with major protocol deviations that impact the evaluability of the results (see Section 10.3 "Protocol Deviations") will be excluded in the PK populations.

10.2 Safety Population

The safety population consists of all the subjects who give informed consent and have at least one exposure to THS 2.2 or NRT gum (including the product test at Admission Day regardless of whether or not they are enrolled in the study).

10.3 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, use of any nicotine tobacco-containing product during wash-out days, assessments not performed or performed

outside the scheduled time windows, or use of oestrogen or other 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 a PK population.

10.3.1 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. 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 9.

Table 9: Definition of Major Protocol Deviations

Category	Description
Violation	Violation of inclusion/exclusion criteria
Mis-randomization	Being administered the wrong product according to the randomization schedule
Mis-use of product	• Use of any nicotine or tobacco–containing product other than the assigned product during the exposure period, or use of any nicotine tobacco-containing product during wash-out days (e.g. see Section 11.4 "Measurements of Product Compliance"). • Use of NRT gum for less than 10 min (i.e., did not chew 2 mg NRT gum for at least 10 min)
Concomitant medication	Use of any drugs which are known to affect CYP2A6 activity

Among the above criteria, violations of inclusion criteria 3, 6 to 8, or of the exclusion criteria 1, 3 to 16, and 18 will be assessed for their impact on the PK population and evaluated during the pre-analysis data review meeting (Section 6.3.1 "Methods of Assigning Subjects to Treatment Sequences").

10.3.2 Minor Protocol Deviations

The categories for the minor deviations will include, but are not limited to the deviations presented in Table 10.

Table 10: Definition of Protocol Deviation Categories

Category	Description
Time deviation (Plasma nicotine PK sample)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 11)
Time deviation (other assessment)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 11)
NRT product use deviation	NRT gum not chewed within the time window 35±5min
Assessment missing (Plasma nicotine PK sample)	Assessment is missing
Assessment missing (other assessment)	Assessment is missing

10.3.2.1 Assessment Windows

Smoking of the randomized product must take place within the 06:00 and 09:00 AM window at Day 1 and Day 3. The windows reported in Table 11 will be applied to the timing of data collection.

Table 11: Definition of Assessment Windows

Assessment	Nominal Time point(s) (relative to T_0)	Window
Plasma nicotine PK sample (THS 2.2 or CC)	First sample 2, 4, 6, 8 and 10 min 15, 30 and 45 min 60 min 2, 4, 6, 9, 12 and 24 h	Within 15 min prior to T_0 + 1 min + 2 min + 3 min + 5 min
Plasma nicotine PK sample (NRT gum)	First sample 10, 20, 25, 30, 35, 40, 45 min 60 min 2, 3, 4, 6, 9, 12 and 24 h	Within 15 min prior to T_0 + 1 min + 3 min + 5 min
Assessment of cough	First assessment 24 h after T_0	Prior to product use - 5 min
QSU-brief (THS 2.2 or CC)	First time 15 min, 30 min, 45 min, 1 h and 2 h 4, 6, 9 and 12 h	Within 15 min prior to T_0 +10 min +10 min
QSU-brief NRT gum	First time 20 min, 30 min, 45 min, 1 h and 2 h 4, 6, 9 and 12 h	Within 15 min prior to T_0 +10 min +10 min
COHb blood sampling	First sample 15 min 60 min 4 and 12 h	Within 15 min prior to T_0 + 2 min + 3 min + 5 min
CO breath test	First measurement Second measurement Third measurement Fourth measurement	Within 15 min prior to T0 12:00-01:30 PM 04:00-05:30 PM 08:00-09:30 PM
CYP2A6	COT and HCOT measurements	Prior to Smoking

11 PLANNED STATISTICAL METHODS

11.1 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 sequence, product, 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, PK data will be summarized and analyzed for the appropriate PK population, biomarker data will be summarized and analyzed for the PK populations unless otherwise stated.

11.1.1 Stratified Presentation

Data summaries will be produced by sequence, sex (male and female), CC nicotine level at Admission (ISO nicotine level ≤0.6 mg and >0.6≤ 1mg), and time point (if applicable), unless otherwise stated.

Stratified presentations will be conducted on the PK populations for the following endpoints:

- Demographics
- Nicotine concentrations in blood
- PK parameters, during single use day
- COHb and CO values, during single use day
- MCEQ and QSU-brief questionnaires, during single use day

11.1.2 Subgroup Analyses

Exploratory subgroup analyses will be conducted for the primary endpoints in the following planned subgroups: sex (male or female), CC nicotine level at Admission (ISO nicotine level ≤0.6 mg and >0.6≤ 1mg) provided there are greater than 4 subjects in each category.

11.1.3 Descriptive Statistics

For continuous data, summary statistics will include the number of subjects, the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum, maximum, and number; for log-normal data (e.g., the PK parameters: AUC and C_{max}) the geometric mean and geometric CV will be presented instead of the arithmetic mean and SD. For categorical data, frequency counts and percentages will be presented.

Data listings will include all subject-level data collected as defined in the protocol.

Summary statistics and statistical analyses will 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 PK population will be produced by analysis group, product, and overall if applicable.

Summaries on Safety population will be produced overall and by sequence, including the available data from subjects who tested the product but were not enrolled or were discontinued from enrollment (back up subjects) before randomization.

The following product labels and sequence descriptions will be used throughout the TFLs (Table 12) :

Table 12: Product and Sequence Labels

Product	Format used in TFLs	Order in TFLs
Tobacco Heating System 2.2	THS 2.2	1
Conventional cigarettes	CC	2
Nicotine replacement therapy gum	NRT gum	3
Sequence		
THS 2.2 then CC	THS 2.2 - CC	1
CC then THS 2.2	CC – THS 2.2	2
THS 2.2 then NRT gum	THS 2.2 – NRT gum	3
NRT gum then THS 2.2	NRT gum – THS 2.2	4

The following stratification labels (Table 13) for the TFLs will be used:

Table 13: Stratification Labels

Stratification Factor	Definition
Sex	male
	female
ISO nicotine level	≤ 0.6 mg
	> 0.6 to ≤ 1.0 mg
	> 1.0 mg[1]

[1] Note that due to inclusion criteria for the study there should not be any subjects with ISO nicotine level > 1.0 mg, therefore this category will not be presented unless there is sufficient data for analysis/presentation (see Section 11.1.5.1 "Insufficient Data for Analysis/Presentation").

11.1.4 Definitions for Statistical Data Analysis

The following definitions (Table 14) for statistical analyses/presentations will be used:

Table 14: Timepoint Definitions

Term	Definition
Baseline	Baseline will be the last available time point prior to the product test (THS 2.2 or NRT gum) at Admission (Day -1)
T_0	The time of the product use on Day 1 and Day 3. Start of product use for THS 2.2 is defined as the time of the first puff. The start time for CC corresponds to the lighting of the CC, and the start time of the NRT gum product is the time of the first NRT gum intake.

11.1.5 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". For the analysis of QSU-brief score for NRT gum as compared to THS 2.2, the QSU-brief values for NRT use at time T_0+15min will be imputed by the QSU-brief values observed at T_0+20min, given the longer t_{max} expected for NRT use.

For the calculation of PK parameters, partial dates/times for PK assessments or T_0 will not in general be imputed. For time points recorded in the format hh:mm, instead of hh:mm:ss, the missing information on seconds will be imputed by 30 sec.

For laboratory parameters:

- For the calculation of summary statistics, values below the LLOQ (BLQ) will be imputed using LLOQ/2 and included in descriptive statistics. Values above ULOQ (AUQ) will be imputed as the ULOQ and included in descriptive statistics.
- Where there is No Result (NR), these are considered as missing, and will not be imputed.
- The number of values below BLQ or AUQ will be presented in each summary table.
- If 50% or more data are BLQ or AUQ, these values will not be imputed and only the number (%) of BLQ or AUQ values will be reported in the summaries, together with minimum (if not BLQ are present) and maximum (if not AUQ are present) of the observed values.

For PK concentration data:

- LLOQ values before T_0 are considered as zero.
- LLOQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC).
- Any other LLOQ value (after T_0 and before the last quantifiable value) would need to be queried and, if confirmed, it will be imputed by LLOQ/2.

11.1.5.1 Insufficient Data for Analysis/Presentation

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

Stratified summaries by sex or nicotine levels will not be presented if less than 4 subjects are available in one sex or nicotine levels strata.

11.1.6 Handling of Unplanned Data

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

11.1.7 Multiple Comparisons / Multiplicity

No formal adjustment of the test-wise alpha level for multiple testing is necessary, as the primary definition of success includes is the precision of the estimates of the primary endpoint and no claim(s) will be made based on the outcome of the individual tests.

11.2 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).

Inclusion and exclusion criteria will be listed as to whether the subjects have met or not met the criteria by sequence, subject, and study day (Screening and Admission).

Subjects in the Safety and PK populations will be displayed by sequence and overall.

All subjects who fail to complete the study will be categorized by their primary reason for discontinuation and summarized by sequence and overall. 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 sequence and overall, 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:

TFL number	Title
TABLES	
15.2.1.1	Summary of Subject Disposition – Screened Population
15.2.1.2	Summary of Reasons for Discontinuations – Randomized Population
15.2.1.3	Summary of Protocol Deviations – Safety Population
LISTINGS	
15.3.1.1	Listing of Inclusion/Exclusion Criteria – Screened Population

TFL number	Title
15.3.1.8	Listing of Subject Disposition and Assignment to Analysis Sets – Screened Population
15.3.2.7	Listing of Subjects and Observations Excluded from Efficacy Analysis
15.3.1.12	Listing of Protocol Deviations – Screened Population
16.1.7	Listing of Randomization Scheme and Codes

11.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety and PK populations, and listed for the Safety population.

The demographic variables age, sex, race, body weight, height and BMI will be summarized by sequence and overall for the Safety population.

Demographics will be tabulated overall and by the two stratification factors (sex and CC nicotine level at Admission) for the PK populations, as specified in Section 11.1.1 "Stratified Presentation".

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – Group-1 PK Population
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-1 PK Population
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-1 PK Population
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – Group-2 PK Population
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-2 PK Population
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-2 PK Population
LISTINGS	
15.3.1.7	Listing of Demographics – Screened Population

11.3.1 CYP2A6 Activity at Admission

CYP2A6 activity will be calculated as the metabolic ratio of trans 3' hydroxycotinine and COT measured at Day -1, as described in Section 7.2.1 "CYP2A6". Data will be listed

and summarized as reported in Section 11.3 "Demographics and Other Baseline Characteristics".

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – Group-1 PK Population
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-1 PK Population
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-1 PK Population
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – Group-2 PK Population
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-2 PK Population
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-2 PK Population
LISTINGS	
15.3.1.11	Listing of CYP2A6 Activity – Safety Population

11.3.2 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 11.3 "Demographics and Other Baseline Characteristics".

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – Group-1 PK Population
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-1 PK Population
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-1 PK Population
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – Group-2 PK Population
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-2 PK Population

TFL number	Title
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-2 PK Population
LISTINGS	
15.3.1.10	Listing of Fagerström Test for Nicotine Dependence Results – Safety Population

11.3.3 Current Cigarette and Smoking Characteristics

The following smoking characteristics at Admission (Day -1) will be summarized and listed as specified in Section 11.3 "Demographics and Other Baseline Characteristics": ISO tar yeld (continuous and categorized as 1-5 mg, 6-8 mg, 9-10 mg and >10 mg), ISO nicotine level (continuous and categorized as ≤ 0.6 mg, > 0.6 to ≤ 1 mg, and > 1 mg), and number of CCs smoked on a daily basis during the previous 4 weeks (categorized as < 10 cig/day, 10-19 cig/day and >19 cig/day).

Current CC brand(s) smoked by the subject and recorded at Admission (Day -1) will be summarized and listed by sequence and study day for the safety population. This will include brand name(s), and ISO nicotine and tar yields. The smoking characteristics and current CC brand collected at Screening Visit 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 sequence at Screening and Admission (Day -1) 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 4 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:

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 – Group-1 PK Population
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-1 PK Population
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-1 PK Population
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – Group-2 PK Population
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex – Group-2 PK Population

TFL number	Title
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level – Group-2 PK Population
15.2.1.5	Summary of Current Cigarette Brands at Admission – Safety Population
LISTINGS	
15.3.1.2	Listing of Current Cigarette Brands – Safety Population
15.3.1.3	Listing of Smoking History – Safety Population
15.3.1.4	Listing of Advice on Risks of Smoking/Smoking Cessation – Safety Population
15.3.1.5	Listing of Product Test, Willingness to Use the Product, Willingness to Quit Smoking, Readiness to Accept Smoking Interruption – Safety Population

11.3.4 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 Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and listed separately by sequence, System Organ Class (SOC) and Preferred Term (PT) within SOC.

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 sequence, SOC and PT within SOC.

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:

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	
15.3.1.9	Listing of Medical History and Concomitant Disease – Safety Population

11.3.5 Other Data

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

- COT urine test
- Urine pregnancy test
- Chest x-ray
- Urine drug screen
- Serology
- Alcohol breath test
- Prior medication
- Product Test and Demonstration
- Identification of NRT gum brand
- Willingness to use THS 2.2 and NRT gum products

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.1	Summary of Subject Disposition – Screened Population
LISTINGS	
15.3.1.5	Listing of Product Test Willingness to Use the Product, Willingness to Quit Smoking, Readiness to Accept Smoking Interruption – Safety Population
15.3.1.6	Listing of Safety Laboratory Entry Criteria – Safety Population
15.3.6.3	Listing of Prior and Concomitant Medication – Safety Population

11.4 Measurements of Product Compliance

Levels of CO in exhaled breath will be measured to evaluate the exposure to CO (see Section 11.6.2.2.1 "Exhaled CO and COHb"), and to monitor compliance during the following study days (see Section 6.3.3 "Compliance to Product Allocation"):

- Wash-out on Day 0 and Day 2
- Single use Day 1 and Day 3 for subjects exposed to NRT gum.

CO data will be listed and summarized by sequence for all study days and timepoints as continuous variable and with the categorization ≤10 ppm and >10 ppm.

Values above 10 ppm will be highlighted in listings and be considered as non compliance if such values are observed prior to first product use on the single use days for all exposures and throughout the single use days for NRT gum exposure. During the washout days values above 10 ppm will be considered non-compliance on Day 2, but will be expected on Day 0 because smoking is ad libitum during Day -1. CO data leading to

exclusion of subjects from the analysis will be evaluated during the pre-analysis blind data review.

Number and percentage of subjects considered as non compliant during the study will be tabulated by sequence and study days for the Randomized population

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.10.1	Descriptive Statistics of Exhaled CO (ppm) During Single Use Continuous Measurements– PK Population
15.2.4.10.1.1	Descriptive Statistics of Exhaled CO (ppm) During Single Use by Sex – PK Population
15.2.4.10.1.2	Descriptive Statistics of Exhaled CO (ppm) During Single Use by Nicotine Level – PK Population
15.2.4.10.2	Descriptive Statistics of Exhaled CO (ppm) During Single Use Categorical Measurements– PK Population
15.2.4.11.1	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 Continuous Measurements– PK Population
15.2.4.11.1.1	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 by Sex – PK Population
15.2.4.11.1.2	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 by Nicotine Level – PK Population
15.2.4.11.2	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 Categorical Measurements– PK Population
15.2.5.1	Descriptive Statistics of Compliance– Randomized Population
LISTINGS	
15.3.3.5	Listing of Exhaled Breath CO (ppm) and Measurement Times – Safety Population

11.5 Extent of Exposure (Product Consumption)

Details of the product test prior to enrollment and of product use after randomization will be listed by sequence for the Safety population.

The number and percentage of subjects who smoked 1, 2, or 3 (categories of 0 and >3 will be included if applicable) THS Tobacco Stick at admission will be tabulated; together with the number and percentage of subjects who performed the NRT gum product trial, chewing for a period of 35±5min (categories of < 10min, ≥10min and <30min, >40min, or not performed will be added if applicable).

The number and percentage of subjects who smoked 0 or 1 (category >1 will be included if applicable) THS Tobacco Stick, or CC during single use days (Day 1 or Day 3) will be tabulated by sequence; together with the number and percentage of subjects who performed the single use day of the NRT gum chewed for a period of 35±5min

(categories of <10min, ≥10min and <30min, >40min, or not performed will be added if applicable).

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.2.1	Descriptive Statistics of Product Use - Safety Population
LISTINGS	
15.3.2.1	Listing of Product Usage – Safety Population
15.3.2.2	Listing of Cigarette Butt and Tobacco Stick Collection Data – Safety Population

11.6 Planned Statistical Analyses

11.6.1 Primary Analyses

The primary parameters C_{max} and $AUC_{(0\text{-last})}$ will be listed and summarized as described in Section 11.1 "General Considerations" and subsections .

Only subjects in the Group-1 PK population who provide evaluable data for both the THS 2.2 and CC products will be included in the following analyses.

The primary analysis of C_{max} and $AUC_{(0\text{-last})}$ will be performed on the natural log-transformed parameters using an analysis of variance (ANOVA) model with terms for sequence, subject nested within sequence, period and product as fixed effect factors (**Senn, 2002**, **FDA, 2001**, **CHMP, 2010,** and **CHMP Appendix IV, 2011**).

Carry-over effect will not be tested, as it cannot be statistically distinguished from the interaction between product and period in a 2x2 crossover design.

The SAS code to be used is shown below:

```
Proc glm data=_data_;
Class subject sequence product period;
Model log_pk = sequence subject(sequence) period product;
Lsmean product / pdiff =control('CC') alpha=0.05 cl;
Run;
```

where "log_pk" is the the natural log-transformed PK parameter being analyzed.

Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis".

LS means for each product will be back-transformed by exponentiation and will be tabulated together with the ratio (THS 2.2 : CC) and 95% CI.

The geometric CV will also be presented as $CV(\%) = 100\sqrt{(e^{MSE} - 1)}$, where MSE is the mean square error of the fitted model residual.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.3.1	Analysis of Primary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population
15.2.3.2	Analysis of Primary Pharmacokinetic Parameters of Nicotine by Sex and Nicotine Level - Group-1 PK Population
15.2.4.5	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine – PK Population
15.2.4.5.1	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Sex – PK Population
15.2.4.5.2	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Nicotine Level – PK Population
FIGURES	
15.1.1.1	Primary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population
LISTINGS	
15.3.3.1	Listing of Pharmacokinetic Parameters of Nicotine – Safety Population
15.3.2.6	Individual Efficacy Response Data – PK Population

11.6.2 Secondary Analyses

11.6.2.1 Pharmacokinetics

The secondary PK parameters from Group-1 PK population ($AUC_{(0\text{-}t')}$, $AUC_{(0\text{-}\infty)}$, $\%AUC_{extrap}$, t_{last}, t_{max}, λ_z and $t_{½}$) and all the PK parameters from Group-2 PK population (C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}t')}$, $AUC_{(0\text{-}\infty)}$, $\%AUC_{extrap}$, t_{last}, t_{max}, λ_z and $t_{½}$) will be listed and summarized as described in Section 11.1 "General Considerations" and subsections. In addition plots of the data versus product will be provided.

The nicotine plasma concentrations will be summarized in a similar manner to the PK parameters but will also be split out by sample time point. Geometric mean (95% CI) profiles, spaghetti plots of all subjects and individual PK profiles for each subject will also be presented.

PK parameter and plasma concentration data will also be listed along with the details of the actual times after T_0.

TFL number	Title
TABLES	
15.2.4.5	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine – PK Population
15.2.4.5.1	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Sex – PK Population
15.2.4.5.2	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Nicotine Level – PK Population
15.2.4.6	Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL)– PK Population
15.2.4.6.1	Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) by Sex – PK Population
15.2.4.6.2	Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) by Nicotine Level – PK Population
FIGURES	
15.1.2.1.1	Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI – Group-1 PK Population
15.1.2.1.2	Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI – Group-2 PK Population
15.1.2.2.1	Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects – Group-1 PK Population
15.1.2.2.2	Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects – Group-2 PK Population
15.1.2.3	Nicotine Plasma Concentration (ng/mL) Profiles by Subject – PK Population
15.1.2.4	Secondary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population
15.1.2.5	Pharmacokinetic Parameters of Nicotine – Group-2 PK Population
LISTINGS	
15.3.3.1	Listing of Pharmacokinetic Parameters of Nicotine – Safety Population
15.3.3.2	Listing of Plasma Nicotine Concentrations (ng/mL) and Sampling Times – Safety Population
15.3.3.3	Listing of Additional Pharmacokinetic Parameter Data – Safety Population

11.6.2.1.1 THS 2.2 vs CC

Only subjects in the Group-1 PK population will be included in the following analyses.

- The secondary analysis of $AUC_{(0-\infty)}$, $AUC_{(0-t')}$ and $t_{½}$ will be performed on the natural log-transformed parameters using the same ANOVA model as used for the primary analysis. (Section 11.6.1 "Primary Analyses"). Only subjects in the Group 1-PK population who provide evaluable data for both the THS 2.2 and CC products will be included in the analyses.

Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis" in order to evaluate the sensitivity of THS 2.2 effect estimates to methods used for missing data by means of a mixed model approach, should there be 20% or more missing parameter PK model.

- The analysis of t_{max} will be performed by calculating the difference for each subject (THS 2.2 - CC) and obtaining the Hodges-Lehmann (**Hodges and Lehmann, 1963**) 95% CI estimates. The median t_{max} for each product and the median difference between the products along with the 95% CI will be presented in the tables. Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis" in order to evaluate the THS 2.2 effect estimates on t_{max} adjusted for period, sequence, and subject within sequence.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.1	Analysis of Secondary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population

11.6.2.1.2 THS 2.2 vs NRT gum

The following analyses will be conducted in only Group-2 PK population:

- The secondary analysis of C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}t')}$ and $t_{½}$ parameters will be performed parameters using the same ANOVA model as used for the primary analysis. (Section 11.6.1 "Primary Analyses").

  Only subjects in the Group-2 PK population who provide evaluable data for both the THS 2.2 and CC products will be included in the analyses.

  The analysis of C_{max} and $AUC_{(0\text{-last})}$ will test if the lower bound of the 95% CI for the ratio (THS 2.2 : NRT gum) is > 1.0 at the 0.025 level of significance in order to determine if the rate and the amount of nicotine absorbed of the THS 2.2 is higher relative to NRT gum. This approach will be used to test the following hypothesis for both C_{max} and $AUC_{(0\text{-last})}$ parameters:

  H_0: $X_{THS} / X_{NRT} = 1.0$
  H_A: $X_{THS} / X_{NRT} > 1.0$

  where X_{THS} and X_{NRT} are the adjusted geometrical means of THS 2.2 and NRT gum, respectively. H_0 is rejected with a type I error $\alpha = 0.025$ (one-sided test).

- To test if the time to the maximum nicotine concentration in THS 2.2 is shorter than in NRT gum the following hypothesis will be evaluated:

  H_0: $X_{THS} - X_{NRT} = 0$

  H_A: $X_{THS} - X_{NRT} < 0$

  where X_{THS} and X_{NRT} are the median values of the THS 2.2 and NRT gum, respectively. t_{max} will be analysed on the original scale using the Wilcoxon Signed-Rank Test with a type I error $\alpha = 0.025$ (one-sided test), as values are ordinal/discrete, and the assumption of normality may be questionable.

  The analysis of t_{max} will be performed by calculating the difference for each subject (THS 2.2 – NRT gum) and obtaining the Hodges-Lehmann 95% CI estimates (**Hodges and Lehmann, 1963**). The median t_{max} for each product and the median difference between the products along with the 95% CI will be presented.

Supportive analysis will be performed as described in Section 11.6.3 "Supportive/Sensitivity Analysis".

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.2	Analysis of Pharmacokinetic Parameters of Nicotine – Group-2 PK Population

11.6.2.2 Biomarkers

11.6.2.2.1 Exhaled CO and COHb

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

CO in exhaled breath will be measured using the Smokerlyzer® device, such as the Micro+™ Smokerlyzer® device or similar, once on Day -1 and Day 4. On Days 1 and 3, the first test per day will be performed within 15 minutes prior to T_0 and then between 12:00 PM and 01:30 PM, between 4:00 PM and 05:30 PM, and between 8:00 PM and 09:30 PM. On the wash-out days (Day 0 and Day 2) it will be conducted between 8:00 AM and 09:30 AM, 12:00 PM and 01:30 PM, between 4:00 PM and 05:30 PM, and between 8:00 PM and 09:30 PM.

Analysis of the COHb measurement will be performed at a local laboratory using blood samples taken at specified timepoints. A total of 5 blood samples will be taken per single use day. The first sample will be taken within 15 minutes prior to T_0. Thereafter the sampling times in relation to T_0 are at 15 minutes, 60 minutes, 4 hours, 12 hours post T_0.

Descriptive statistics summarized by exposure will be produced separately for all scheduled timepoints for exhaled CO and COHb assessments at single use day. This will be done on the PK populations, overall and by the two stratification factors (sex, CC nicotine level at Admission) as specified in Section 11.1.1 "Stratified Presentation".

Actual values of blood COHb and levels of exhaled CO will be listed and summarized. The number of subjects with COHb levels ≤2% will be summarized for each measurement. The 2% threshold is important because, as reported in (**WHO, 2010**), COHb elevated above 2% was found to cause ST-segment changes and decreased time to angina.

In addition line graphs will be produced for exposure means (and 95% CI) over all timepoints.

Values of exhaled CO measured during wash-out, Admission, and discharge will not be analyzed because they will be collected only for monitoring purposes, however they will be reported as described in Section 11.4 "Measurements of Product Compliance".

The analysis of the exhaled CO during single use and log transformed blood COHb levels will be performed using a mixed effects ANOVA with a restricted maximum likelihood (REML) method to estimate mean differences and variances separately for THS 2.2 vs CC and THS 2.2 vs NRT gum, using heterogeneous compound symmetry covariance structure in order to allow unequal variances at the different timepoints (**Brown and Prescott, 1999**). Subjects nested within sequence will be used as a random effects and sequence, period, product and product*time point as fixed effect factors. The model will be evaluated including all of the different assessment timepoints, excluding the assessment prior to T_0, In addition, time point will be treated as a repeated measurement.

The SAS code to be used is shown below:

```
Proc mixed data=_data_ method=reml maxiter=200;
Class subject sequence product period;
Model log_COHb (or CO) = sequence period product time_point
product*time_point;
Random subject(sequence);
Repeated time_point / subject=subject*product type=csh;
Lsmean product / pdiff =control('CC/NRT') alpha=0.05 cl;
Lsmean product*time_point / pdiff alpha=0.05 cl;
Run;
```

In case of model convergence issues, this will be reported in the study report and additional covariance structures will be investigated with the following order: heterogeneous autoregressive(type=arh), variance component (type=vc), and unstructured (type=un).

For the analysis of CO breath test, the main comparison will be the difference over all time points. LS means for each product, the overall difference (THS 2.2 - CC or THS 2.2

- NRT gum as appropriate) and the differences at each time point will be presented in the tables as a point and interval (95% CI) estimate. Figures of the LS mean difference and 95% CI at each time point will be produced.

For the COHb analysis, the main comparison will be the ratio over all time points. LS means for each product will be back-transformed by exponantiation and presented in tables together with the point and interval (95% CI) estimate of the overall ratio (THS 2.2:CC or THS 2.2: NRT gum as appropriate) and of the ratios at the different time points.Figures of the LS mean ratio and 95% CI at each time point will be produced.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.7	Analysis of Blood COHb (%) – PK Population
15.2.4.8.1	Descriptive Statistics of Blood COHb (%) Continuous Measurements – PK Population
15.2.4.8.1.1	Descriptive Statistics of Blood COHb (%) by Sex – PK Population
15.2.4.8.1.2	Descriptive Statistics of Blood COHb (%) by Nicotine Level – PK Population
15.2.4.8.2	Descriptive Statistics of Blood COHb (%) Categorical Measurements – PK Population
15.2.4.9	Analysis of Exhaled CO (ppm) During Single Use – PK Population
15.2.4.10.1	Descriptive Statistics of Exhaled CO (ppm) During Single Use Continuous Measurements – PK Population
15.2.4.10.1.1	Descriptive Statistics of Exhaled CO (ppm) During Single Use by Sex – PK Population
15.2.4.10.1.2	Descriptive Statistics of Exhaled CO (ppm) During Single Use by Nicotine Level – PK Population
15.2.4.10.2	Descriptive Statistics of Exhaled CO (ppm) During Single Use Categorical Measurements– PK Population
15.2.4.11.1	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 Continuous Measurements – PK Population
15.2.4.11.1.1	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 by Sex – PK Population
15.2.4.11.1.2	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 by Nicotine Level – PK Population
15.2.4.11.2	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 Categorical Measurements– PK Population
FIGURES	
15.1.2.6.1	Blood COHb (%) Profiles Geometric Mean and 95% CI – Group-1 PK Population
15.1.2.6.2	Blood COHb (%) Profiles Geometric Mean and 95% CI – Group-2 PK Population

TFL number	Title
15.1.2.7.1	Blood COHb (%) Profiles Geometric Least Squares Mean Ratio and 95% CI – Group-1 PK Population
15.1.2.7.2	Blood COHb (%) Profiles Geometric Least Squares Mean Ratio and 95% CI – Group-2 PK Population
15.1.2.8.1	Exhaled CO (ppm) Profiles During Single Use Arithmetic Mean and 95% CI – Group-1 PK Population
15.1.2.8.2	Exhaled CO (ppm) Profiles During Single Use Arithmetic Mean and 95% CI – Group-2 PK Population
15.1.2.9.1	Exhaled CO (ppm) Profiles During Single Use Arithmetic Least Squares Mean Differences and 95% CI – Group-1 PK Population
15.1.2.9.2	Exhaled CO (ppm) Profiles During Single Use Arithmetic Least Squares Mean Differences and 95% CI – Group-2 PK Population
LISTINGS	
15.3.3.4	Listing of Blood COHb Levels (%) and Sampling Times – Safety Population
15.3.3.5	Listing of Exhaled Breath CO (ppm) and Measurement Times – Safety Population

11.6.2.3 Questionnaires

11.6.2.3.1 Urge-to-Smoke Questionnaire of Smoking Urges Brief

The total score and the two factors from the QSU-brief will be listed for all scheduled time points and summarized overall and by the two stratification factors (sex, CC nicotine level at Admission) for the PK populations, as specified in Section 11.1.1 "Stratified Presentation". The individual responses to all questions will be listed by product, study day, and assessment time points.

In addition line graphs will be produced for the total score and factors means (and 95% CI) over all timepoints.

The analysis of the subjective effects of smoking (the total score, and Factor-1 and Factor-2 from the QSU-brief) will be performed using the same mixed effects ANOVA adopted for the analysis of CO breath test described in Section 11.6.2.2.1 "Exhaled CO and COHb". The time points of the THS 2.2 assessment schedule will be considered in the analysis, and data at T_0+15min for NRT gum will be imputed as described in Section 11.1.5 "Handling of Dropouts or Missing Data (including outside the limits of quantification)".

A sensitivity analysis using bootstrap techniques, will also be conducted on the total and factors score of QSU-brief, as described in Section 11.6.3 "Supportive/Sensitivity Analysis".

The main comparison will be the mean difference over all timepoints. LS means for each product, the overall mean difference (THS 2.2 - CC or THS 2.2 - NRT gum as appropriate) and the mean differences at each time point will be presented in the tables as

a point and interval (95% CI) estimate. Figures of the LS mean difference and 95% CI at each time point will be produced.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.12	Analysis of QSU-brief Questionnaire Factors and Total Score – PK Population
15.2.4.15	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score – PK Population
15.2.4.15.1	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score by Sex – PK Population
15.2.4.15.2	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score by Nicotine Level – PK Population
FIGURES	
15.1.2.10.1	QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI – Group-1 PK Population
15.1.2.10.2	QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI – Group-2 PK Population
15.1.2.11.1	QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences and 95% CI – Group-1 PK Population
15.1.2.11.2	QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences and 95% CI – Group-2 PK Population
LISTINGS	
15.3.6.11	Listing of QSU-brief Questionnaire Results – Safety Population

11.6.2.3.2 Modified Cigarette Evaluation Questionnaire

The MCEQ domain scores composed of the three multi-item subscales and two single items from the MCEQ will be listed and summarized overall and by the two stratification factors (sex, CC nicotine level at Admission) for the PK populations, as specified in Section 11.1.1 "Stratified Presentation". The individual responses to all questions will be listed.

A mixed effects ANOVA model will be used to estimate mean THS 2.2-CC differences of the MCEQ domain scores and variances, with a REML method, using heterogeneous compound symmetry covariance structure (**Brown and Prescott, 1999**). Subjects within sequence will be used as random effects and fixed effects are period, sequence, and product exposure.

```
Proc mixed data=_data_ method=reml maxiter=200;
Class subject sequence product period;
Model response = sequence period product;
Random subject(sequence) / subject=subject type=csh;
Lsmean product / pdiff =control('CC/NRT') alpha=0.05 cl;
Run;
```

In case of model convergence issues, additional covariance structures will be investigated with the following order: heterogeneous autoregressive(type=arh), variance component (type=vc), and unspecified (type=un).

LS means for each product and the overall point and 95% interval estimate of the difference (THS 2.2 - CC) will be presented in the tables.

A sensitivity analysis using bootstrap techniques, will also be conducted on the MCEQ domain scores, as described in Section 11.6.3 "Supportive/Sensitivity Analysis".

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.16	Analysis of MCEQ Subscales – PK Population
15.2.4.17	Analysis of MCEQ Subscales by Bootstrapping Techniques – PK Population
15.2.4.18	Descriptive Statistics of MCEQ Subscales – PK Population
15.2.4.18.1	Descriptive Statistics of MCEQ Subscales by Sex – PK Population
15.2.4.18.2	Descriptive Statistics of MCEQ Subscales by Nicotine Level – PK Population
LISTINGS	
15.3.6.12	Listing of MCEQ Questionnaire Results – Safety Population

11.6.3 Supportive/Sensitivity Analysis

To support the interpretation of the PK analysis, the values of nicotine concentration greater than BLOQ before T_0 will be listed together with any PK parameters excluded from the analysis. Listing will be presented by PK parameter impact, sequence, period and study date.

To better understand the impact of the higher than expected T_0 values, an analysis of the PK parameters will be performed as described above, however the data for subjects with their T_0 value >5% of their C_{max} value will be excluded from the analysis.

Sensitivity analysis will be conducted on the C_{max} and $AUC_{(0\text{-last})}$ endpoints for the Group-1 and Group-2 PK populations should there be 20% or more missing PK parameter values. This analysis is conducted on all the available PK parameters and subjects will be excluded from the analysis if the nicotine concentration T_0 value is >5% of their C_{max} value. The analysis will be conducted in the natural log scale using the same

mixed effects ANOVA model described in Section 11.6.2.3.2 "Modified Cigarette Evaluation Questionnaire". Point and 95% interval estimates of the ratios will be back-transformed by exponentiation and tabulated.

The same sensitivity analysis for C_{max} and $AUC_{(0\text{-last})}$ endpoints will be conducted on t_{max}, in both Group-1 and Group-2 PK populations, supporting with THS 2.2 effect estimates on t_{max} adjusted for period, sequence, and subject within sequence.

In case any time information is imputed for the computation of PK parameters as described in Section 11.1.5 "Handling of Dropouts or Missing Data (including outside the limits of quantification)" in any PK population, the median t_{max} for THS 2.2 will be calculated following the imputation of missing time data by 0 sec and 30 sec. If the difference between the two median t_{max} is larger than 5%, a supportive analysis will be conducted by repeating the analyses described in Section 11.6.1 "Primary Analyses" and 11.6.2 "Pharmacokinetics" on the t_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-t'})}$ endpoints estimated by means of the imputation of missing time by 0 sec.

To evaluate the sensitivity to the distributional assumptions for the QSU-brief (see Section 11.6.2.3.1 "Urge-to-Smoke Questionnaire of Smoking Urges Brief") and MCEQ (see Section 11.6.2.3.2 "Modified Cigarette Evaluation Questionnaire") questionnaire scores, point and 95% interval estimates will also be assessed by means of the percentile bootstrap technique, using 2000 bootstrap samples which preserve the number of subjects per sequence.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.3.1	Supportive Analysis of Pharmacokinetic Parameters of Nicotine Excluding Subjects with T_0 Value >5% of Their C_{max} Value – PK Population
15.2.4.3.2	Analysis of Pharmacokinetic Parameters of Nicotine by Bootstrapping Techniques –PK Population
15.2.4.4	Analysis of Pharmacokinetic Parameters of Nicotine by Zero Sec Imputation –PK Population
15.2.4.14	Analysis of QSU-brief Questionnaire Factors and Total Score by Bootstrapping Techniques – PK Population
15.2.4.17	Analysis of MCEQ Subscales by Bootstrapping Techniques – PK Population

11.6.4 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 11.1.3 "Descriptive Statistics".

11.6.4.1 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 signing of informed consent will be recorded electronically. 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). All AEs occurred after the product test of THS 2.2 or NRT gum will be included in the summary tables. During the screening period prior to the first THS 2.2 or NRT gum product use, only study procedure related AEs will be included in the summary tables.

AEs reported from subjects that have a first product use, but were not randomized will be summarized in a separate sequence: "Exposed but not randomized". The remainder of safety endpoints assessed in enrolled subjects that have a first product use, but were not randomized will be summarized in a separate sequence: "Enrolled but not randomized".

Partial dates will not be imputed, but assumptions will be made as follows to assign to exposure-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.	Exposure-emergent
Partial date, e.g., --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening.	Not exposure-emergent

11.6.4.2 Adverse Events

A general summary table of AEs will be presented by sequence and overall, 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, related to NRT gum) and expectedness (expected, not expected).
- The number of events and the number and percentage of subjects reporting at least one AE broken down by severity, including a subject once with worst severity.
- 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 (combining the following items: product use interrupted, product use

reduced, product use stopped), 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 by sequence and overall, with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by SOC and PT coded according to the 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) and reference point product (NRT gum).
- 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 for each sequence, with the worst occurrence based on the presentation (e.g., for presentation by severity = most severe, for presentation by relationship = most related). Missing information on the intensity of AE will be counted as severe.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.1	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 Reference Point Product (NRT gum) – Safety Population
15.2.6.4	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.6.5	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.6.6	Summary of Adverse Events Related to Study Procedure by System

TFL number	Title
	Organ Class and Preferred Term – Safety Population
LISTINGS	
15.3.6.1.1	Listing of Adverse Events – Screened Population

11.6.4.2.1 Serious Adverse Events (Including Deaths)

A general summary table of SAEs will be presented by sequence and overall, including the number of events and the number and percentage of subjects reporting at least one SAE.

SAEs will be listed in separate listings by sequence.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.1	Summary of Adverse Events – Safety Population
LISTINGS	
15.3.6.1.2	Listing of Serious Adverse Events – Screened Population

11.6.4.2.2 Adverse Events Leading to Withdrawal

Summaries will be presented for AEs leading to withdrawal, by sequence and overall as described in Section 11.6.4.2 "Adverse Events".

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.1	Summary of Adverse Events – Safety Population
LISTINGS	
15.3.6.1.3	Listing of Adverse Events Leading to Discontinuation – Safety Population

11.6.4.2.3 Laboratory Abnormalities

Laboratory abnormality data will be listed ordered by sequence, product, subject and time point. Details related to the toxicity grading of laboratory abnormalities are available in Section 11.6.4.4 "Clinical Laboratory Evaluation".

TFL number	Title
LISTINGS	
15.3.6.4	Listing of Clinical Chemistry Data, Shift, Changes from Baseline and

TFL number	Title
	CTCAE grades – Safety Population
15.3.6.5	Listing of Hematology Data Shift, Changes from Baseline and CTCAE grades – Safety Population
15.3.6.6	Listing of Urinalysis Data Shift, Changes from Baseline and CTCAE grades – Safety Population
15.3.6.1.3	Listing of Adverse Events Leading to Discontinuation – Safety Population

11.6.4.3 THS 2.2 Device Events

All events relating to the THS 2.2 device 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 sequence and overall, 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 sequence. Data collected during Screening will be listed but not summarized.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.7	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 – Safety Population

11.6.4.4 Clinical Laboratory Evaluation

Table 15 lists the hematology, clinical chemistry, and urine analysis parameters to be assessed in this study.

Table 15: List of Laboratory Safety Parameters

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

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

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

Laboratory data will be summarized and listed at baseline (Admission, Day -1) and at discharge (Day 4 or at the day of withdrawal), together with changes from baseline. The number and percentage of subjects with normal results, high/low results and abnormal clinical result (as defined by PI comment) 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 defined by the PI comments), 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:

TFL number	Title
TABLES	
15.2.6.10	Summary of Clinical Chemistry Parameters – Safety Population
15.2.6.11	Summary of Hematology Parameters – Safety Population
15.2.6.12	Summary of Urinalysis Parameters – Safety Population

TFL number	Title
LISTINGS	
15.3.6.4	Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades – Safety Population
15.3.6.5	Listing of Hematology Data Shift, Changes from Baseline and CTCAE grades – Safety Population
15.3.6.6	Listing of Urinalysis Data Shift, Changes from Baseline and CTCAE grades – Safety Population

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

11.6.4.5.1 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 sequence using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization - Drug Dictionary Enhanced [WHO-DDE] Q1 2013). 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 sequence. Concomitant medications will be summarized for the Safety population showing the number (%) of subjects who used the medication at least once by sequence and by ATC 1st and 2nd levels medical term and by preferred drug name. Listings will be provided by sequence and will display original dates (no imputation).

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.8.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population

TFL number	Title
15.2.6.8.2	Summary of Prior Medication by Preferred Drug Name – Safety Population
15.2.6.9.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.6.9.2	Summary of Concomitant Medication by Preferred Drug Name – Safety Population
LISTINGS	
15.3.6.3	Listing of Prior and Concomitant Medication – Safety Population

11.6.4.5.2 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -1) and at discharge (Day 4 or at the day of withdrawal for withdrawn subjects) will be listed by sequence. Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. Number of subjects (%) with normal, abnormal, and abnormal clinically significant results will be tabulated by body systems at Screening, baseline (Admission), and discharge.

Body weight recorded at Admission and 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 7.4 "Categorical Variables"), at Admission and discharge, will be presented by sequence and overall.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.16	Summary of Weight and BMI Measurements – Safety Population
15.2.6.17	Summary of Physical Examination of Body Systems – Safety Population
LISTINGS	
15.3.6.10	Listing of Physical Examination Findings, Shift and Changes from Screening – Safety Population

11.6.4.5.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate measured during the study will be listed by sequence and study day.

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

The data will be presented in the below outputs:

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

11.6.4.5.4 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, Admission and discharge. At Screening, data are collected prior and post-bronchodilator, also including the brand(trade) name and dose of the bronchodilator.

Spirometry data values and normality evaluation will be listed by sequence and study day. Assessments performed after baseline (Admission, Day -1) will be listed together with change from baseline and shift in normality. Spirometry data from subjects who had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for FEV_1(L), FEV_1 (% pred), FVC(L), FVC(% pred), and FEV_1/FVC at baseline, and discharge by sequence, and overall. Spirometry 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:

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

11.6.4.5.5 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; heart rate; and normality evaluation (normal, abnormal, abnormal clinically relevant, together with any PI comments to the abnormality). In addition the QTcF value will be presented.

ECG data values and normality evaluations will be listed by sequence and study day (Screening, Day 1, and Day 3) together with changes and shift in normality from baseline (Screening). ECG data from subjects which had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for ECG data at baseline, Day 1, and Day 3 by sequence and overall. ECG data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinical significant results.

The data will be presented in the below outputs:

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

11.6.4.5.6 Assessment of Cough

Cough questionnaire is assessed from Day 0 to Day 4, prior to product use on Day 1 and Day 3. Questionnaire details are reported in Section 7.3.4 "Cough Assessment".

The number and % of subjects reporting a cough will be summarized by sequence and overall. 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 sequence and overall, for all subjects who filled in the questionnaire. The answers to the open question related to any other important observation will be listed.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.6.18	Summary of Cough Assessments – Safety Population
15.2.6.18.1	Summary of Cough Assessments by Study Day – Safety Population
LISTINGS	
15.3.6.13	Listing of Cough Assessment Results – Safety Population

12 ANALYSIS AND REPORTING

12.1 Interim Analysis and Data Monitoring

No interim analysis is planned on this study.

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

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

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

12.2 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
15.2.2.1	Descriptive Statistics of Product Use - 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 Product Exposure for Investigational Product (THS 2.2 or CC) and Reference Point Product (NRT gum) – Safety Population
15.2.6.7	Summary of THS 2.2 Device Events – Safety Population
LISTINGS	
15.3.6.1.2	Listing of Serious Adverse Events – Safety Population
15.3.6.1.3	Listing of Adverse Events Leading to Discontinuation – Safety Population

12.3 Topline Results

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

TFL no.	Title
TABLES	
15.2.3.1	Analysis of Primary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population
15.2.4.1	Analysis of Secondary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population
15.2.4.2	Analysis of Pharmacokinetic Parameters of Nicotine – Group-2 PK Population
15.2.4.5	Descriptive Statistics of the Pharmacokinetic Parameters of Nicotine – PK Population
15.2.4.6	Descriptive Statistics of Plasma Nicotine Concentrations – PK Population
15.2.4.12	Analysis of QSU-brief Questionnaire Factors and Total Score – PK Population
15.2.4.15	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score – PK 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
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics – Group-1 PK Population
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics – Group-2 PK Population
FIGURES	
15.1.1.1	Primary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population
15.1.2.1.1	Nicotine Plasma Concentration (units) Profiles Geometric Mean and 95% CI Group-1 PK Population
15.1.2.1.2	Nicotine Plasma Concentration (units) Profiles Geometric Mean and 95% CI Group-2 PK Population
15.1.2.10.1	QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI – Group-1 PK Population
15.1.2.10.2	QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI – Group-2 PK Population
15.1.2.11.1	QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences and 95% CI – Group-1 PK Population
15.1.2.11.2	QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences and 95% CI – Group-2 PK Population

12.4 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.

12.5 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	
15.2.1.1	Subject Disposition – Screened Population
15.2.4.19	Descriptive Statistics of Sex, Age, and Nicotine Level – PK Population
15.2.3.3	Analysis of Pharmacokinetic Parameters of Nicotine C_{max}, $AUC_{(0\text{-last})}$, t_{max} – PK Population

13 DATA PRESENTATION

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

14 REFERENCES

Beal, 1989

Beal SL. Sample Size Determination for Confidence Intervals on the Population Means and on the Difference between Two Population Means. 1989; Biometrics, 45, 969–977.

Bennowitz et al, 2002

SNRT subcommittee on biochemical verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002;4(2):149-159.

Brown and Prescott, 1999

Brown H, Prescott R. Applied Mixed Models in Medicine. Wiley, 1999; Ch 6.

C54451/Medical_Device_Problem_Codes_FDA_CDRH

United States Food and Drug Administration. Implementation Specifications, reporting medical device problems, C54451/Medical Device Problem Codes, FDA, CDRH. Available from http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/EventProblemCodes/ucm135741.htm (accessed on 04 October 2012)

Chemical Information Specialized Information Services RN:486-56-6

http://chem.sis.nlm.nih.gov/chemidplus/cas/486-56-6 (accessed on 15 July 2013)

Chemical Information Specialized Information Services RN:34834-67-8

http://chem.sis.nlm.nih.gov/chemidplus/cas/34834-67-8 (accessed on 15 July 2013)

Cappelleri et al, 2007

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007;32(5):912-923.

CHMP, 2010

The Committee for Medicinal Products for Human Use (CHMP) Guideline on the Investigation of Bioequivalence, 20 January 2010

CHMP Appendix IV, 2011

The Appendix IV of the CHMP Guideline on the Investigation on Bioequivalence, 17 Novemeber 2011

Cox et al, 2001

Cox LS, Tiffany ST, Christen AG (2001) Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res 3(1):7–16

Dautzenberg et al., 2007

Bertrand Dautzenberg, Mitchell Nides, Jean-Luc Kienzler and Anne Callens. Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell®). BMC Clinical Pharmacology 2007, 7:11 doi:10.1186/1472-6904-7-11. Available at http://www.biomedcentral.com/content/pdf/1472-6904-7-11.pdf (accessed on 01 February 2013)

Fagerström et al, 2012

Fagerström K, Russ C, Yu C, Yunis C and Foulds J. The Fagerström Test for Nicotine Dependence as a Predictor of Smoking Abstinence: A Pooled Analysis of Varenicline Clinical Trial. Nicotine & Tobacco Research. 2012; first published online March 30, 2012

FDA, 2001

Food and Drug Administration (FDA) Guidance to Industry for Statistical Approaches to Establishing Bioequivalence, January 2001

Heatherton et al, 1991

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991;86(9):1119-1127.

Hodges and Lehmann, 1963

Hodges, J. L.; Lehmann, E. L. (1963). "Estimation of location based on ranks". Annals of Mathematical Statistics 34 (2): 598–611.

Hu and Cassano, 2000

Guizhou Hu and Patricia A. Cassano. Antioxidant Nutrients and Pulmonary Function: The Third National Health and Nutrition Examination Survey (NHANES III). Am. J. Epidemiol. (2000) 151 (10): 975-981.
Available from http://aje.oxfordjournals.org/content/151/10/975.full.pdf (accessed 26 Jul 2013)

ICH Guideline E3, 1995

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

ICH Guideline E9, 1998

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

Jacob et al, 2011

Jacob P 3rd, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL. Determination of the Nicotine Metabolites Cotinine and Trans-3'-Hydroxycotinine in Biologic fluids of Smokers and Non-smokers using Liquid Chromatography - Tandem Mass Spectrometry: Biomarkers for Tobacco Smoke Exposure and for Phenotyping Cytochrome P450 2A6 Activity. J Chromatogr B Analyt Technol Biomed Life Sci. 2011 Feb 1;879(3-4):267-276.

Lehmann, 1975

Lehmann EL. Nonparametrics: Statistical Methods Based on Ranks. New York: McGraw-Hill, 1975; Chs 3 & 4.

Sasaki H, Nakamura M et al., 2001

Standard value of the spirogram and partial pressure of arterial blood gas in Japanese. Lung Physiology Expert Committee Report, The Japanese Respiratory Society

Senn, 2002

Senn S. Cross-over Trials in Clinical Research. 2002; John Wiley & Sons.ISBN: 978-0-471-49653-3

Snedecor and Cochran, 1982

Snedecor GW, Cochran WG. Statistical Methods (8th edition). Iowa: Iowa State Univ Press, 1982: 217-253.

WHO, 2010

WHO Guidelines for Indoor Air Quality: Selected Pollutants, WHO (2010) ISBN 978 92 890 0213 4

ZRHX-PK-02, 2012

Philip Morris International, Switzerland. 2012. Clinical study. A Single-center, Open-label, Randomized, Controlled, Crossover Study to Explore the Nicotine Pharmacokinetic Profile and Safety of Tobacco Heating System (THS) 2.1 Compared to Conventional Cigarettes Following Single and ad Libitum Use in Smoking, But Otherwise Healthy Subjects. Available at http://clinicaltrials.gov/ct2/show/NCT01780688?term=NCT01780688&rank=1

15 APPENDICES

15.1 Study Assessments

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge [k]	Safety follow-up [l]
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Informed consent/ subject information sheet	•							
Advice on the risks of smoking and debriefing	•	•					•	
Inclusion/exclusion criteria	•	•						
Enrolment		•						
Randomization			•					
Product demonstration of THS 2.2 and NRT gum	•							
Product test for THS 2.2 and NRT gum		•						
Product use				•		•		
Support during periods of reduced smoking/smoking abstinence (as required)			•	•	•	•		
Identification of current CC brand	•	•						
Smoking history	•	•						

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge [k]	Safety follow-up [l]
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Readiness to abstain from smoking for up to 4 days	•	•						
Willingness to quit smoking in the next 3 months	•							
Demographics [a], medical history, concomitant diseases	•							
Prior medication [b] / Concomitant medication	•	•	•	•	•	•	•	•
Physical examination, body height, weight and related BMI [c]	•	•					•	
Vital signs [d]	•	•	•	•	•	•	•	
ECG	•			•		•		
Spirometry	•	•					•	
Chest X-ray [e]	•							
B/U:Haematology, clinical chemistry, urine analysis	•	•					•	
B: Serology	•							
U: Urine drug screen, urine cotinine screen	•	•						
Alcohol test	•	•						
U: Pregnancy test (females)	•	•					•	

	Screening	Admission	Wash-out	Single use	Wash-out	Single use	Day of Discharge [k]	Safety follow-up [l]
Study Day	**-29 to -2**	**-1**	**0**	**1**	**2**	**3**	**4**	**4 to 11**
Collection of used Tobacco Sticks and CC butts and NRT gum				•		•		
B: Plasma nicotine [f]				•	•	•	•	
B: COHb [g]				• (5x)		• (5x)		
CO breath test [h]		• (1x)	• (4x)	• (4x)	• (4x)	• (4x)	• (1x)	
B: *trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma		•						
FTND questionnaire	•							
QSU–brief questionnaire [i]				•		•		
MCEQ (modified version, only after THS 2.2 and CC use				•		•		
Cough assessment [j]			•	•	•	•	•	
AE/SAE recording	•	•	•	•	•	•	•	•

See also instructions and abbreviations on the following page.

Abbreviations: AE = Adverse event; CC = conventional cigarette(s); CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP2A6 = Cytochrome P450 2A6; ECG = Electrocardiogram; FTND = Fagerström Test for Nicotine Dependence (revised version); MCEQ = Modified Cigarette Evaluation Questionnaire; NRT gum = Nicotine replacement therapy gum; QSU-brief = Questionnaire of Smoking Urges; SAE = Serious adverse event; THS = Tobacco Heating System

B : Blood sample required. U : Urine sample required.

a: Sex, date of birth/age, race.

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

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

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

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

f: Nicotine blood samples to be taken as follows:

Single Use on Day 1 and Day 3 for THS 2.2 and CC only:

For subjects on THS 2.2 or on CC, a total of 16 blood samples will be taken for a 24-hour profile (Day 1 and Day 3). The first blood sample will be taken within 15 minutes prior to the single use (T_0). Times of sampling are thereafter in relation to T_0: T_1 after 2 minutes + 1 min, T_2 after 4 minutes + 1 min, T_3 after 6 minutes + 1 min, T_4 after 8 minutes + 1 min, T_5 after 10 minutes + 1 min, T_6 after 15 minutes + 2 min, T_7 after 30 minutes + 2 min, T_8 after 45 minutes + 2 min, T_9 after 60 minutes + 3 min, T_{10} after 2 hours + 5 min, T_{11} after 4 hours + 5 min, T_{12} after 6 hours + 5 min, T_{13} after 9 hours + 5 min, T_{14} after 12 hours + 5 min, and T_{15} after 24 hours + 5 min (this sample will be drawn during the day following product use, i.e., wash-out).

Single Use on Day 1 and Day 3 for NRT gum only:

For subjects on NRT gum: A total of 16 blood samples will be taken for a 24-hour profile (Day 1 and Day 3). The first blood sample will be taken within 15 min T_0, Thereafter in relation to T_0: T_1' after 10 min + 1 min, T_2' after 20 minutes + 1 min, T_3' after 25 minutes + 1 min, T_4' after 30 minutes + 1 min, T_5' after 35 minutes + 1 min; T_6' after 40 minutes + 1 min; T_7' after 45 minutes + 1 min, T_8' after 60 minutes + 3 min, T_9' after 2 hours + 5 min, T_{10}' after 3 hours + 5 min, T_{11}' after 4 hours + 5 min, T_{12}' after 6 hours + 5 min, T_{13}' after 9 hours + 5 min, T_{14}' after 12 hours + 5 min, and T_{15}' after 24 hours + 5 min (this sample will be drawn during the day following product use, i.e., wash-out).

g: COHb blood samples to be taken as follows:

Single use: A total of 5 blood samples will be taken. The first sample within 15 minutes prior to T_0 (start of single product use); thereafter in relation to T_0 at 15 min +2 min, 60 min +3 min, 4 hours +5 min and 12 hours +5 min

h: A CO breath test will be conducted once on Day -1 and Day 4. On Day 0, Day 1, Day 2, Day 3, four breath tests will be done per day. On Day 1 and Day 3, the first test per day will be performed within 15 minutes prior to T_0 (T_0 = start of first product use) and then around 12:00 pm, 4:00 pm and 8:00 pm. On the wash-out days (Day 0 and Day 2) it will be conducted around 8:00 am, 12:00 pm, 4:00pm, and 8:00 pm.

i: QSU–brief will be assessed as follows:

Single use: The QSU-brief will be completed by the subject himself/herself at single use study days.

THS 2.2 and CC arms: First sample within 15 min prior to T_0, 9 assessments thereafter in relation to T_0: 15 min, 30 min, 45 min, 60 min, 2 hr, 4 hrs, 6 hrs, 9 hrs, and 12 hrs after T_0 with a time window of 10 minutes each.

NRT arm: First sample within 15 min prior to T_0, 9 assessments thereafter in relation to T_0: 20 min, 30 min, 45 min, 60 min, 2 hr, 4 hr, 6 hrs, 9 hrs, and 12 hrs after T_0 with a time window of 10 minutes.

j: Visual analogue scale, three Likert scales and one open question. Cough questionnaire should be asked on Day 0 between 06:30 and '09:00, on Day 2 24 hours after T_0 of Day 1, on Day 4, 24 hours after T_0 of Day 3, and on Day 1 and Day 3, prior product use.

k: All examinations listed at the Day of Discharge should also be conducted in subjects preliminarily terminating the study.

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