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PMI RESEARCH & DEVELOPMENT

Clinical Study Report

ZRHM-PK-05-JP

Study Title:	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum
Short Title:	Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Number:	ZRHM-PK-05-JP
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	01 August 2013
Study Completed (last subject last visit):	16 November 2013
Principal Investigator and Affiliation:	F. Nobuoka, MD Ageo Medical Clinic 3133 Haraichi, Ageo City Saitama 362-0021, Japan
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Sponsor Signatories:	Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist Nicola Lama, PhD, Biostatistician Andrea Donelli, Clinical Scientist Patrick Picavet, MD, Medical Safety Officer
Version:	1.0
Date:	12 May 2015

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

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

**SYNOPSIS**

Sponsor: Phillip Morris Products S.A.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)	Volume:	
Name of Active Ingredient: Not applicable	Page:	
Study Title: A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum.		
Principal Investigator and Study Center: F. Nobuoka, MD, Ageo Medical Clinic, 3133 Haraichi, Ageo City, Saitama 362-0021, Japan		
Publication (reference): ClinicalTrials.gov ID: NCT01967706. Brief Title: Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)		
Period of Study: First subject screened: 01 August 2013 Last subject completed: 16 November 2013		
Objectives and Endpoints: Primary Objective and Endpoints: The primary objective of this study was: <ol style="list-style-type: none">To evaluate the rate and the amount of nicotine absorbed (as assessed by maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC] from start of product use to the time of the last quantifiable concentration [$AUC_{(0-last)}$]) from THS 2.2 Menthol relative to menthol conventional cigarettes (mCC), following single use of THS 2.2 Menthol and mCC. <u>Endpoints:</u> Nicotine pharmacokinetic (PK) parameters (THS 2.2 Menthol vs. mCC): <ul style="list-style-type: none">C_{max}AUC_{0-last} Secondary Objectives and Endpoints: The secondary objectives of this study were: <ol style="list-style-type: none">To determine if C_{max} and $AUC_{(0-last)}$ of plasma nicotine of the THS 2.2 Menthol are higher relative to nicotine replacement therapy (NRT) gum following single use of the THS 2.2 Menthol and NRT gum. <u>Endpoints:</u> Primary nicotine PK parameters (THS 2.2 Menthol vs. NRT gum): <ul style="list-style-type: none">C_{max}AUC_{0-last} <ol style="list-style-type: none">To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to infinity [$AUC_{(0-\infty)}$] and AUC from start of product use to the subject-specific time of maximum nicotine concentration following single use of the mCC or NRT gum product [$AUC_{(0-t^*)}$]) between the THS 2.2 Menthol and mCC, as well as the THS 2.2 Menthol and NRT gum.		

Endpoints:

Secondary nicotine PK parameters:

- $AUC_{(0-\infty)}$.
- Partial $AUC_{(0-t^*)}$.

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

Endpoint:

- $t_{1/2}$

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

Endpoints:

Urge-to-smoke questionnaire (Questionnaire of Smoking Urges-brief [QSU-brief]):

- Total score
- Factor 1
- Factor 2

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

Endpoints:

Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]):

- 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 Menthol, as compared to mCC 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 Menthol malfunction/misuse.
- Respiratory symptoms: cough assessment by Visual Analogue Scale (VAS) and Likert scales and 1 open question.
- Vital signs.
- Spirometry.
- Electrocardiogram (ECG).
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medications.

**Methodology:****Study design:**

This was a randomized, controlled, 2-period, 4-sequence, single use crossover study where each subject received 2 of the following 3 products:

- THS 2.2 Menthol.
- mCC.
- NRT gum.

The study was performed during a 6 day confinement period (5 overnight stays).

Day -29 to Day -2:

A Screening Visit was conducted within 4 weeks prior to Admission to the investigational site (Day -29 to Day -2). A demonstration of the THS 2.2 Menthol and the NRT gum was performed by the study site collaborator during the Screening Visit.

Day -1 (Admission Day):

As the last procedure of the eligibility assessments, all subjects performed a product test prior to enrollment: first THS 2.2 Menthol (using up to 3 Menthol Tobacco Sticks) and subsequently NRT gum. Product tests with either the THS 2.2 Menthol or the NRT gum were only performed in female subjects with a negative urine pregnancy test. Only subjects willing and ready to use both the THS 2.2 Menthol and NRT gum were enrolled in order to minimize the dropout rate during the course of the study.

Day 0 to Day 3 (Confinement period):

The confinement consisted of 2 periods (Period 1, Period 2), with each period consisting of at least a 24 hour nicotine wash-out (nicotine abstinence) and 1 day of single product use.

Period 1: Day 0: Wash-out; Day 1: single product use (THS 2.2 Menthol/mCC/NRT gum).

Period 2: Day 2: Wash-out; Day 3: single product use (THS 2.2 Menthol/mCC/NRT gum).

In total, 62 eligible, mCC-smoking subjects were randomized into 1 of the 4 sequences:

- Sequence 1: THS 2.2 Menthol → mCC (N=22).
- Sequence 2: mCC → THS 2.2 Menthol (N=22).
- Sequence 3: THS 2.2 Menthol → NRT gum (N=9).
- Sequence 4: NRT gum → THS 2.2 Menthol (N=9).

Subjects were discharged from the investigational site the morning of the Day 4 following the completion of all examinations of the Day of Discharge.

Day 4 to Day 11 (Safety Follow-up Period):

After discharge, there was a 7-day safety follow-up period to record spontaneously reported new adverse events (AEs)/serious adverse events (SAEs) and the active follow-up of ongoing AEs/SAEs by the site. End of study was defined as the last day of the 7 day safety follow up subsequent to discharge from the clinic.

Type of blinding: This was an open-label study; subjects and investigators were unblinded to subjects' sequence. However, there was a limited degree of blinding in the data review and data analysis process. Part of the Sponsor and the Clinical Research Organization personnel were blinded to the randomized sequence, with blinded and unblinded personnel roles and processes defined by the data review plan.

**Number of Subjects (Planned and Analyzed):**

Planned:	62 subjects
Screened:	147 subjects
Exposed to THS 2.2 Menthol:	73 subjects
Enrolled:	73 subjects
Randomized:	62 subjects
Safety population	73 subjects
Group-1 PK population:	43 subjects
Group-2 PK population	18 subjects

The Group-1 (comparison between THS 2.2 Menthol and mCC) and Group-2 (comparison between THS 2.2 Menthol and NRT gum) PK populations were composed of a different set of subjects.

Diagnosis and Main Criteria for Inclusion:

Sixty-two smoking healthy adult Japanese subjects, who met the following main inclusion criteria:

- Subject was aged from 23 to 65 years (inclusive).
- Subject was Japanese.
- Subject was a smoking, healthy subject, as judged by the Principal Investigator, based on all available assessments in the Screening period/Day of Admission (e.g., safety laboratory, spirometry [forced expiratory volume in 1 second {FEV₁}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV₁ >80% predicted value, and post-bronchodilator FVC >0.8], vital signs, physical examination, ECG, chest X-ray and medical history).
- Subject was smoking at least 10 commercially available mCC per day (no brand restrictions) with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO)/mCC, as labeled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject had been smoking for at least the last 3 consecutive years. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- The subject did not plan to quit smoking in the next 3 months.
- The subject was willing and able to accept interruptions of smoking for up to 4 days.
- The subject was willing and able to accept using both the THS 2.2 Menthol and NRT gum products.

Subjects who did not complete the study after randomization were not replaced.

Test Product and Lot Numbers:

The THS 2.2 Menthol product was provided by the sponsor and comprised the following components: THS Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.

Pack batch number of THS Menthol Tobacco Sticks: B-05775. Production date: 12 June 2013. Expiry date: 11 January 2014.

Duration of Exposure Period:

The exposure period was the period after randomization and consisted of 2 periods (Period 1, Period 2), with each period comprising of at least a 24-hour nicotine wash-out (nicotine abstinence) and 1 day of single product use THS 2.2 Menthol, and mCC or NRT gum.

Reference Products:

The subject's own supply of commercially available single-brand of mCC of up to 1 mg nicotine ISO per cigarette. Nicotine replacement therapy gum (Nicorette® 2 mg gum) was used as a non-investigational reference point product.

Statistical Methods:**Pharmacokinetic Data**

The primary analysis was performed on the natural log-transformed PK parameters (C_{max} and AUC_(0-last)) using an analysis of variance (ANOVA) model in the Group-1 PK population. The model included terms for sequence, subject nested within sequence, period, and product as fixed effect factors. The least squares



(LS) means for each product was back transformed by exponentiation and tabulated together with the ratio (THS 2.2 Menthol : mCC) and 95% confidence interval (CI).

Exploratory sub-group analyses were conducted for the primary endpoints in the following 2 planned sub-groups: sex and nicotine levels (≤ 0.6 mg and >0.6 mg to ≤ 1 mg). The primary analysis was repeated for each level of the 2 sub-groups.

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

The analyses of $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and $t_{1/2}$ for the comparison between THS 2.2 Menthol and mCC (Group-1 PK population) and the comparison between THS 2.2 and NRT gum (Group-2 PK population) (plus C_{max} and $AUC_{(0-last)}$ for the Group-2 PK population) were performed on the natural log-transformed parameters using the same ANOVA model as used for the primary analysis.

The analysis of t_{max} was performed by calculating the difference for each subject (THS 2.2 Menthol - mCC or THS 2.2 Menthol - NRT gum) and obtaining the Hodges-Lehmann 95% CI estimates. The median t_{max} for each product and the median difference between the products along with the 95% CI was calculated.

The analysis of C_{max} and $AUC_{(0-last)}$ tested if the lower bound of the 95% CI for the ratio (THS 2.2 Menthol : NRT gum) was >1.0 with a one-sided significance level of 2.5% in order to determine if the rate and the amount of nicotine absorbed from THS 2.2 Menthol were higher relative to NRT gum.

The parameter t_{max} was analyzed to test if it was shorter with THS 2.2 Menthol than with NRT gum and was analyzed on the original scale using the Wilcoxon Signed-Rank Test

To support the interpretation of the PK analysis, the values of nicotine concentration greater than the lower limit of quantification before T_0 were listed together with any PK parameters excluded from the analysis. Listings were presented by PK parameter impact, sequence, period, and study date.

To better understand the impact of the T_0 value $>5\%$ of their C_{max} values, an analysis of the PK parameters excluding these subjects was performed as described above for the primary analysis.

Study Hypotheses And Evaluation Criteria

The primary objective of this study was to determine the point estimate and precision of the nicotine relative bioavailability (ratio of THS 2.2 Menthol:mCC) for C_{max} and $AUC_{(0-last)}$, therefore, there was no statistical hypothesis to be tested for the primary objective.

For the secondary objectives the following hypotheses were examined for THS 2.2 Menthol versus NRT gum analyses:

- The geometric mean C_{max} for THS 2.2 Menthol was higher relative to NRT gum.
- The $AUC_{(0-last)}$ for THS 2.2 Menthol was larger relative to NRT gum.
- The median t_{max} for THS 2.2 Menthol was shorter than for NRT gum.

The study evaluation criteria were defined as 95% CI of the THS 2.2 Menthol:mCC ratio for the nicotine C_{max} and $AUC_{(0-last)}$ being estimated with a precision of $\pm 20\%$, based on the level of variability expected from the previous study (ClinicalTrials.gov Identifier: NCT01780688).

Exhaled CO and Blood COHb Data

The exhaled CO and blood COHb were analyzed using a mixed-effects ANOVA with a restricted maximum likelihood (REML) method to estimate mean differences and variances separately for THS 2.2 Menthol vs mCC and THS 2.2 Menthol vs NRT gum, using heterogeneous compound symmetry covariance structure in order to allow unequal variances at the different time points. Subject nested within sequence was used as a random effects and sequence, period, product, and product*time point as fixed effect factors. The model was evaluated including all of the different assessment time points, excluding the assessment prior to T_0 . In addition, time point was treated as a repeated measurement.

Subjective Effects Questionnaire Data

The QSU-brief questionnaire scores were analyzed using the same mixed-effects ANOVA adopted for the



analysis of CO breath test.

A mixed-effects ANOVA model was used to estimate mean THS 2.2 Menthol - mCC differences of the MCEQ domain scores and variances, with a REML method, using variance component covariance structure. Subjects within sequence were used as random effects and fixed effects were period, sequence, and product exposure.

Safety Data

There was no formal statistical analysis of safety data. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA[®], Version 16.0). Adverse Events were listed by sequence and summarized by sequence, severity, relationship, and expectedness to product or study procedures. Serious AEs were listed separately. Adverse events were categorized by system organ class (SOC) and preferred term (PT). Respiratory symptoms (cough assessment), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), spirometry, ECG data, clinical laboratory safety panel (clinical chemistry, hematology, and urine analysis), body mass index, physical examination, and device malfunction/misuse events were listed and summarized.

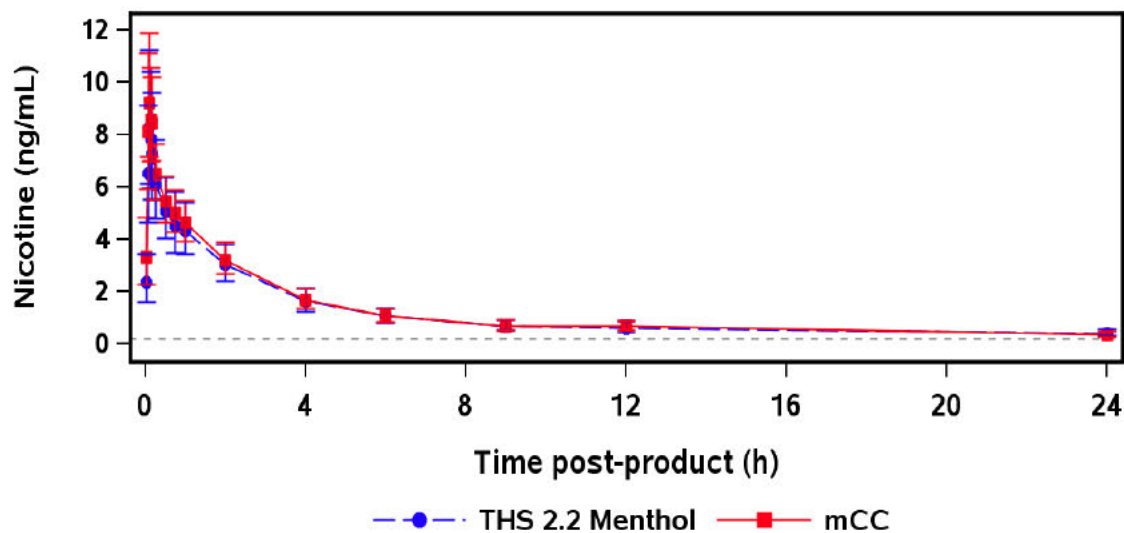
Medical History and concomitant disease were coded using MedDRA Version 16.0 and listed separately by sequence, SOC, and PT within SOC.

All medications were listed and summarized by sequence using PT and Anatomical, Therapeutic Chemical (ATC) codes (World Health Organisation Drug Dictionary, Q1 2013) for the safety population.

Summary of Results

Primary Endpoints

The overall shape of the mean nicotine concentration-time curves was similar for THS 2.2 Menthol and mCC. The plasma concentration versus time profiles following single use of THS 2.2 Menthol and mCC were characterized by a rapid absorption phase, with C_{max} reached at the same time post-product use (6 minutes).



----- Lower limit of quantification (0.2 ng/mL)



Primary Pharmacokinetic Parameters							
PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:mCC) (%)	CV (%)	95% CI	Precision (%)
C _{max} (ng/mL)	THS 2.2 Menthol	43	10.7	88	64	69, 114	26
	mCC	43	12.1				
AUC _(0-last) (ng.h/mL)	THS 2.2 Menthol	43	24.0	98	48	81, 119	21
	mCC	43	24.50				

Abbreviations: AUC_(0-last) = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; CC = conventional cigarette; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; LS = least squares; THS 2.2 = Tobacco Heating System 2.2.

Following single use, there was no notable difference in the nicotine absorption between THS 2.2 Menthol and mCC as assessed by C_{\max} (THS 2.2 Menthol:mCC geometric LS mean ratio: 88%) and $AUC_{(0-\text{last})}$ (THS 2.2 Menthol:mCC geometric LS mean ratio: 98%), with the 95% CIs for both parameters spanning 100%.

High between-subject variability was noted for both C_{\max} and $AUC_{(0-\text{last})}$ for both products, with CV% values ranging from 88% to 117% and 83% to 110%, respectively. The within-subject variability was high for both C_{\max} (64%) and $AUC_{(0-\text{last})}$ (48%).

The THS 2.2 Menthol:mCC ratio for $AUC_{(0-last)}$ was estimated with a precision of 21%, while the precision for C_{max} was 26%, with precision calculated as the largest difference between the 95% CI bounds and the mean.

Secondary Endpoints

Secondary Pharmacokinetic Parameters - THS 2.2 Menthol versus mCC

There was no notable difference in the amount of nicotine absorbed between THS 2.2 Menthol and mCC as assessed by AUC_(0-∞) (THS 2.2 Menthol: 26.3 ng h/mL; mCC: 27.7 ng h/mL; THS 2.2 Menthol:mCC ratio: 95%; 95% CI: 78, 116). The amount of nicotine absorbed as assessed by AUC_(0-t) was lower for THS 2.2 Menthol compared to mCC (THS 2.2 Menthol: 0.6 ng h/mL; mCC: 0.8 ng h/mL; THS 2.2 Menthol:mCC ratio: 74%; 95% CI: 57, 97).

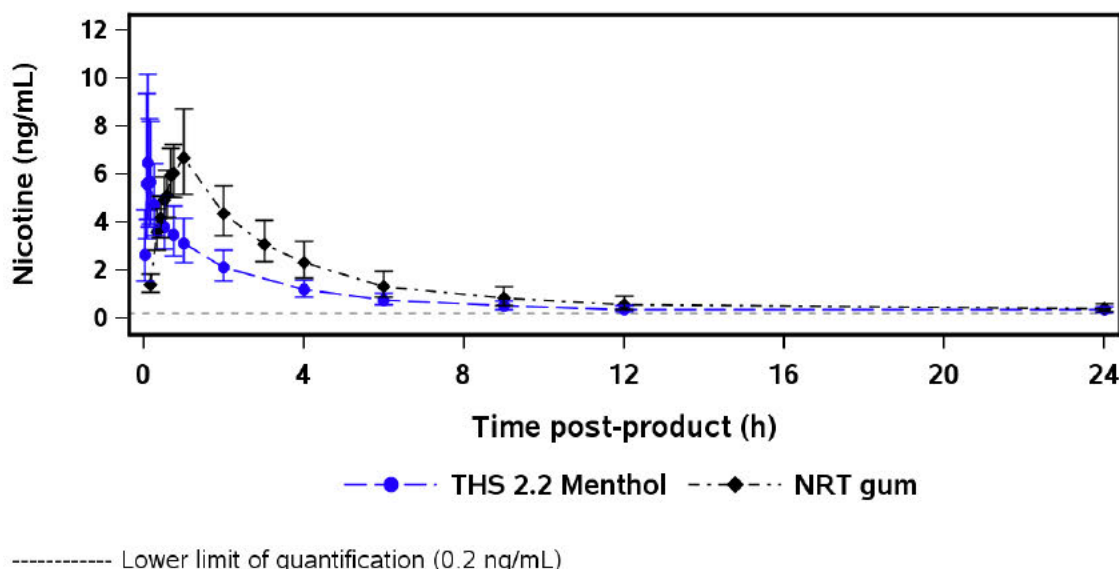
High between-subject variability was noted for both $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ for both products, with CV% values ranging from 85% to 86% and 98% to 160%, respectively. The within-subject variability was high for both $AUC_{(0-\infty)}$ (42%) and $AUC_{(0-t)}$ (67%).

The $t_{1/2}$ was similar for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 4.1 hours (95% CI: 3.6, 4.7) and 4.0 hours (95% CI: 3.5, 4.6) for mCC, with a THS 2.2 Menthol mCC ratio of 102% (95% CI: 85, 123).

For t_{\max} , there was no notable difference between THS 2.2 Menthol and mCC, with a median value of 6 minutes for both products.

**Nicotine Pharmacokinetic Endpoints Following Single Use of THS 2.2 Menthol and NRT Gum**

The overall shape of the mean nicotine concentration-time curves was different for THS 2.2 menthol and NRT gum. The plasma concentration versus time profile following single use was characterized by a rapid absorption phase for THS 2.2 Menthol, while C_{\max} was comparable but attained later following NRT gum use.



Following single use, the maximum exposure to nicotine as assessed by C_{\max} was comparable between THS 2.2 Menthol and NRT gum (THS 2.2 Menthol: 7.6 ng/mL; NRT gum: 7.5 ng/mL; THS 2.2 Menthol:NRT gum ratio: 102%; 95% CI: 62, 166; $P = 0.47$). The amount of nicotine absorbed as assessed by $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ were significantly lower for THS 2.2 Menthol compared to NRT gum ($AUC_{(0-\text{last})}$ THS 2.2 Menthol: 15.6 ng.h/mL; NRT gum: 27.9 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 56%; 95% CI: 38, 81. $AUC_{(0-\infty)}$ THS 2.2 Menthol: 15.8 ng h/mL; NRT gum: 31.1 ng h/mL; THS 2.2 Menthol:NRT gum ratio: 51%; 95% CI: 35, 74. P values were >0.99 for both $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ for the one-sided tests that the exposure was greater for THS 2.2 Menthol compared to NRT gum). The amount of nicotine absorbed as assessed by $AUC_{(0-t)}$ was higher for THS 2.2 Menthol compared to NRT gum but did not achieve statistical significance (THS 2.2 Menthol: 3.4 ng h/mL; NRT gum: 3.0 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 114%; 95% CI: 79, 163; $P = 0.23$).

High between-subject variability was reported for C_{\max} , $AUC_{(0-\text{last})}$, $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$ for both THS 2.2 Menthol and NRT gum, with CV% values ranging from 75% to 109% for THS 2.2 Menthol and 51% to 75% for NRT gum. The within-subject variability was high for C_{\max} , $AUC_{(0-\text{last})}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ (51% to 79%).

The $t_{1/2}$ was comparable for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 3.2 hours (95% CI: 2.7, 3.8) and 3.5 hours (95% CI: 3.0, 4.1) for NRT gum and a geometric mean ratio of 92% (95% CI: 74, 115).

The t_{\max} was significantly shorter for THS 2.2 Menthol (8 minutes) compared to NRT gum (45 minutes), with a median difference of -38 minutes (95% CI: -45, -32, $P < 0.01$).

**Subjective Effects of Smoking Endpoints:****Urge-to-Smoke Symptoms (QSU-brief)**

The average Group-1 PK population urge-to-smoke total score dropped by a maximum of approximately 35% at $T_0 + 15$ minutes and 29% at $T_0 + 30$ minutes following THS 2.2 Menthol and mCC use, respectively, corresponding to maximum reductions of 1.52 and 1.28 point decreases from baseline, respectively. For both THS 2.2 Menthol and mCC, the average total score had not returned to baseline values by the last assessment time point at 12 hours post-product use (90% and 93% of baseline, respectively).

There was no notable difference in QSU-brief total for THS 2.2 Menthol compared to mCC, with an LS mean difference over all time points of -0.3 points for THS 2.2 Menthol - mCC following single use (95% CI: -0.8, 0.2). Consistent results were obtained for the 2 factors, Factor 1 reflecting the desire and intention to smoke with smoking perceived as rewarding (THS 2.2 Menthol - mCC difference of -0.3 (95% CI: -0.9, 0.3); and Factor 2 reflecting anticipation of relief from negative effects of not smoking (THS 2.2 Menthol - mCC difference of -0.2 (95% CI: -0.8, 0.3). The difference between THS 2.2 Menthol and mCC for the total score was greatest at $T_0 + 15$ minutes with a THS 2.2 Menthol - mCC difference of -0.4 (95% CI -1.1, 0.3).

In the Group-2 PK population, the average urge-to-smoke total score dropped by approximately 28% and 22% following THS 2.2 Menthol and NRT gum use, respectively. For THS 2.2 Menthol, the maximum decrease was observed at $T_0 + 30$ minutes and at $T_0 + 45$ minutes for NRT gum, with maximum reductions corresponding to a 1.1 and 0.9 point decrease from baseline, respectively. The average total scores for both products were below their respective baseline values at 12 hours post-product use (95% and 90% for THS 2.2 Menthol and NRT gum, respectively).

There was no notable difference in QSU-brief total score for THS 2.2 Menthol compared to NRT gum, with an LS mean difference over all time points of -0.3 points for THS 2.2 Menthol - NRT gum following single use (95% CI: -0.9, 0.2). Consistent results were obtained for the 2 factors, Factor 1 THS 2.2 Menthol - NRT gum difference of -0.3 (95% CI: -1.0, 0.4), and Factor 2 THS 2.2 Menthol - NRT gum difference of -0.4 (95% CI: -0.7, -0.1). The difference between THS 2.2 Menthol and NRT gum for the total score was greatest at $T_0 + 15$ and 20 minutes, where the applicable assessment time points apply for the products, with a THS 2.2 Menthol - NRT gum difference of -0.8 (95% CI -1.7, 0.1).

Product evaluation questionnaire (MCEQ)

Based on the results from the product comparison using the MCEQ subscale scores following single use, differences were observed for two subscales, with enjoyment of respiratory tract sensation being 0.6 points (95% CI: 0.1, 1.1) lower and smoking satisfaction being 1.1 points (95% CI: 0.7, 1.5) lower for THS 2.2 Menthol compared to mCC.

There was no notable difference in aversion, craving reduction, and psychological reward between THS 2.2 Menthol and mCC following single use, with aversion being 0.1 points (95% CI: -0.4, 0.6) lower, craving reduction being 0.1 points (95% CI: -0.3, 0.5) lower, and psychological reward being 0.2 points lower (95% CI: 0.0, 0.4) for THS 2.2 Menthol than mCC.

Biomarker Endpoints:**Blood COHb**

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.5% for both THS 2.2 Menthol and mCC. Fifteen minutes after product use, the mean value had increased to 3.5% for mCC, while COHb remained stable for the 12 hour post-product evaluation period for THS 2.2 Menthol users (within the range of 2.4% to 2.6%, with the maximum achieved at $T_0 + 60$ minutes). Across the full 12 hour post-product evaluation period, the THS 2.2 Menthol mCC ratio for COHb was 81% (95% CI: 79, 84) after single use.

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.4% for both THS 2.2 Menthol and NRT gum. Following THS 2.2 Menthol and NRT gum use, there was no



notable difference in overall mean COHb levels between THS 2.2 Menthol and NRT gum users. Mean COHb levels remained relatively unchanged throughout the assessment day (2.4% to 2.5% for THS 2.2 Menthol and 2.4% to 2.5% for NRT gum), with the maximum COHb value achieved at T₀ + 4 hours for both products.

Exhaled CO

Mean exhaled CO values following 24 hours of smoking abstinence and prior to product use were 3.5 ppm for THS 2.2 Menthol and 3.7 ppm for mCC. Following single mCC use, the mean exhaled CO levels initially increased, reaching a peak of 5.8 ppm at 12:00-01:30 pm (the first post-product use assessment). Following single THS 2.2 Menthol use, mean CO levels remained relatively steady throughout the evaluation period (within the range of 3.2 to 3.7 ppm with the maximum mean level attained at 04:00-05:30 PM). Across the full post-product evaluation period, the LS mean level for exhaled CO following single THS 2.2 Menthol use was 1.6 ppm lower than that determined following single mCC use (95% CI: 1.3, 1.9).

Mean exhaled CO values following at least 24 hours of smoking abstinence and prior to product use were 3.7 ppm for both THS 2.2 Menthol and NRT gum. Following THS 2.2 Menthol and NRT gum use, there was no notable difference in overall exhaled CO levels. For both products, mean exhaled CO values remained relatively steady throughout the evaluation period (2.9 to 3.7 ppm for THS 2.2 Menthol and 2.7 to 3.3 ppm for NRT gum) with values comparable to baseline observed at 08:00-09:30 PM (3.7 ppm for THS 2.2 Menthol and 3.3 ppm for NRT gum).

Safety:

There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE.

Overall, there were only 4 AEs (lymphocyte count increased, bilirubin conjugated increased, blood bilirubin increased, and hemoglobin decreased) reported by 4 of the 73 subjects (5.5%) in the safety population (which included 11 subjects who were enrolled but not randomized). All 4 AEs were mild in severity. None of the subjects who were exposed but not randomized reported an AE. No AEs were assessed as being related to investigational product (THS 2.2 Menthol or mCC), NRT gum, or study procedures.

None of the subjects experienced a device event or malfunction.

CONCLUSIONS

In this study, the amount of nicotine absorbed was comparable following THS 2.2 Menthol single use when compared to mCC single use. Nicotine was absorbed and eliminated at a similar rate for the 2 products. The results for mCC were consistent with what has previously been reported in the literature. THS 2.2 Menthol single use decreased the urge-to-smoke in a comparable fashion to mCC single use at any time point post-product use. Results from other subjective effects of smoking suggested that THS 2.2 Menthol use was less satisfying and provided a less enjoyable respiratory tract sensation compared to mCC. No notable difference was observed between the 2 products in aversion and psychological reward.

This study demonstrated that nicotine was absorbed more rapidly following THS 2.2 Menthol compared to NRT gum. However, it was also observed that the amount of nicotine absorbed was significantly lower following THS 2.2 Menthol compared to NRT gum, while the elimination rate was comparable for the 2 products. THS 2.2 Menthol use reduced craving faster than NRT gum, but the overall time profile showed no notable difference in urge-to-smoke between THS 2.2 Menthol and NRT gum use. However, THS 2.2 Menthol use decreased the urge-to-smoke more than NRT gum use for the first 4 hours post-product use.

In contrast to mCC single use, where CO exposure increased rapidly, no increase in CO exposure was observed following THS 2.2 Menthol or NRT gum single use.

No SAEs or severe AEs were reported during this study, with no AEs related to investigational product use.

Final Report Date: Version 1.0 / 12 May 2015



Prepared in: Microsoft Word 2010



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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

λ_z	Terminal elimination rate constant
%AUC _{extrap}	Percentage of area under the plasma concentration-time curve that is due to extrapolation from time of the last quantifiable concentration to infinity
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical, Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
AUC _(0-∞)	Area under plasma concentration-time curve from start of product use extrapolated from time of the last quantifiable concentration to infinity
AUC _(0-last)	Area under plasma concentration-time curve from start of product use to time of last quantifiable concentration
AUC _(0-t')	Area under plasma concentration-time curve where t' is the subject-specific time of maximum nicotine concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CC	Conventional cigarette
CI	confidence interval
C _{last}	Last quantifiable concentration
C _{max}	Maximum plasma concentration
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRA	Clinical Research Associate



CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DMP	Data Management Plan
ECG	Electrocardiogram
ePRO	Electronic patient reported outcomes
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GVP	Gas vapor phase
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LS	Least squares
mCC	Menthol conventional cigarette



MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
M RTP	Modified risk tobacco product
NNS	Nicotine nasal spray
NRT	Nicotine replacement therapy
OTC	Over-the-counter
PK	Pharmacokinetic
PMI	Philip Morris International
PT	Preferred term
QC	Quality Control
QSU-brief	Questionnaire of Smoking Urges-brief
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard Operating Procedures
t'	Subject-specific time of peak nicotine concentration
T_0	Time point of first product use during study day
$t_{1/2}$	Terminal half-life
t_{last}	Time of the last quantifiable concentration
THS	Tobacco Heating System
t_{max}	Time to maximum plasma concentration
TPM	Total particulate matter
VAS	Visual Analogue Scale



WBC	White blood cell
WHO-DDE	World Health Organization - Drug Dictionary Enhanced



4 DEFINITION OF TERMS

The following special terms are used in this report.

Charger	The function of the Charger (Model 4) was to recharge the Holder after use. It contained a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around and could itself be recharged from a main power source.
Concomitant medication	The term 'concomitant medication' refers to all medication taken during the study conduct period from the Informed Consent Form (ICF) signature onwards.
Conventional cigarette (CC) and menthol conventional cigarette (mCC)	The term 'conventional cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products. Menthol CC was designated 'mCC' in this study.
Day of Discharge	Day 4.
End of study	'End of study' was defined as the last day of the 7-day safety follow-up subsequent to discharge from the unit.
Enrollment	On Day -1 for eligible subjects after all application inclusion and exclusion criteria had been satisfactorily met and the subject was willing and ready to use both the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) and nicotine replacement therapy (NRT) gum. The test of both THS 2.2 Menthol and NRT gum were the last assessments prior to enrollment.
First product use time point	Start of product use for THS 2.2 Menthol was defined as the time of the first puff. The start time for mCC corresponded to the lighting of the mCC, and the start time of the NRT gum product was the time of NRT gum intake.
Randomization	Assignment to product on Day 0 utilizing an Interactive Web and Voice Response System.
Randomized subject	'Randomized subject' refers to a subject who signed the ICF, met all inclusion/exclusion criteria, and was randomized to 1 of the study sequences via an Interactive Web and Voice Response System.



Safety follow-up period	After the time of discharge, a 7-day safety follow-up was done for the recording of spontaneously reported new adverse events (AEs)/serious adverse events (SAEs) and the active follow-up of ongoing AEs/SAEs by the site. In general any AE was followed up until resolved or stabilized i.e., no worsening of the event or a plausible explanation for the event had been found.
Screening failure	Subjects who did not meet the entry criteria from ICF signature to the time of enrollment were considered a screening failure and were replaced by other subjects.
Screening visit	‘Screening visit’ refers to the visit during which subjects signed the ICF, underwent screening procedures and were reviewed for eligibility.
Sponsor	‘Sponsor’ refers to Philip Morris Products S.A.
Subject	‘Subject’ refers to an individual who participated in the clinical study.
THS Menthol Tobacco Stick (Menthol Tobacco Stick)	The Menthol Tobacco Stick (product code C3 Menthol) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder.
Tobacco Stick Holder (Holder)	The function of the Holder (model 4.2) is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Menthol Tobacco Stick).
Time of Discharge	Time when the subject was released from the site after all the procedures of the Day of Discharge were conducted.
Tobacco Heating Device	The device comprises everything in THS 2.2 Menthol except the Menthol Tobacco Stick.
Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)	THS 2.2 Menthol is composed of the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.



5 ETHICS

5.1 Institutional Review Board

Prior to the start of the study, the clinical study protocol, together with its associated documents (Informed Consent Form [ICF] which included both subject information sheet and informed consent, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Principal Investigator's curriculum vitae and/or other evidence of qualifications, the list of sub Investigators, and any other documents requested by the Institutional Review Board [IRB]), were submitted for review and approval to the relevant IRB. The IRB was appropriately constituted and performed its functions in accordance with the International Conference on Harmonisation (ICH) Tripartite Guidance for Good Clinical Practice (GCP), Ministerial Ordinance on GCP for Drugs, and local requirements, as applicable.

In accordance with GCP, a written confirmation of the IRB approval was provided to the Sponsor. This identified the study (Principal Investigator's name, study number, and title) and the documents that were approved by the IRB, with dates and version numbers, as well as the date of approval. The composition of the IRB, including the name and occupation of the chairperson, was supplied to the Sponsor together with a GCP compliance statement.

Institutional Review Board approval was granted on 04 July 2013. The written approval from the IRB was filed in the Investigator file, and another copy was filed in the Study Master File. The study started after the Sponsor had obtained written confirmation of favorable opinion/approval from the concerned IRB. Relevant safety information was submitted to the IRB during the course of the study in accordance with national regulations and requirements. No protocol amendments occurred during this study.

A copy of the final protocol (Version 1.0 dated 21 June 2013) is provided in [Appendix 16.1.1](#).

The name and address of the IRB are provided in [Appendix 16.1.3](#), together with IRB approval documentation.

5.2 Ethical Conduct of the Study

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, 2008 [1] and are consistent with the applicable ICH/GCP regulatory principles.

The Principal Investigator agreed to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IRB. The Principal Investigator



and the Sponsor signed the protocol to confirm this agreement. A copy of the Declaration of Helsinki, 2008 [1] was placed in the Investigator's Study File.

5.3 Subject Information and Consent

Before or at Screening, the Principal Investigator ensured that each subject was given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study and the Principal Investigator answered all questions the subject had to his/her full satisfaction. Subjects were instructed that they were free to withdraw their consent and discontinue their participation in the study at any time. Subjects were given time for consideration and had the opportunity to ask questions.

The ICF was signed and personally dated by the subject, and by the person who conducted the informed consent discussion. The original signed ICF was stored in the Investigator file and a copy of the signed ICF was given to the subject. No study-specific procedures were performed before the ICF had been signed.

The subject was informed that additional data analyses, not mentioned in the protocol or the Statistical Analysis Plan (SAP), might be performed with the collected data at a later time. If any additional analyses were performed, they were to be fully covered by data confidentiality, as for the main analyses described in the protocol.



6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Principal Investigator, site of study and responsible personnel are listed below.

Study site (clinical conduct)	Ageo Medical Clinic 3133 Haraichi Ageo City Saitama 362-0021, Japan
Principal Investigator	Fumimasa Nobuoka, MD
Sponsor	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Manager Zurich Clinical Program, Clinical Scientist	Christelle Haziza, PhD
Clinical Scientist	Andrea Donelli
Medical Safety Officer	Patrick Picavet, MD (as of 27 March 2015) Kausar Aamir, MD, PhD (until 27 March 2015) Tamara Koval, MD (until 23 October 2014)
Biostatistician	Nicola Lama, PhD
Clinical Study Manager	Muriel Benzimra, MSc
Study Data Manager	Kishor Lad
Clinical laboratory and analytical sites	
Clinical Safety Laboratory	(b) (4)
Carboxyhemoglobin (COHb)	Tokiwa Chemical Industries co., Ltd. 16-22, Kamiikebukuro 4-chome, Toshima-ku Tokyo 170-0012, Japan
Study Coordinator	Chikako Oosaki
Nicotine concentrations and cytochrome p450 (CYP) 2A6 activity	Celerion (USA) 621 Rose Street Lincoln Nebraska 68502 USA
Bioanalysis Principal Investigator	Kirk Newland, BSc
Quality Assurance Manager	Crystal Bickford, BA



Clinical Research Organization (study monitoring)	(b) (4) (b) (4)
Project Leader	(b) (4)
Randomization Interactive Web and Voice Response System	(b) (4)
Project Manager	(b) (4)
Electronic patient reported outcomes (ePRO)	(b) (4)
Senior Project Manager	(b) (4)
Clinical Research Organization (serious adverse event and pregnancy reporting)	United BioSource Corporation (UBC) 16 Chemin des Coquelicots 1214 Vernier/Geneva Switzerland
Safety Scientist	Alexandra Banderier
Clinical Research Organization (data management and study reporting)	Covance CRU Ltd. Springfield House Hyde Street Leeds, LS2 9LH, UK
Project Manager	Kilda Russum, BSc
Medical Monitor	Luke Chung, MD, MPH
Data Manager	Paul Hope, BSc
Pharmacokineticist	Stuart Hossack, BSc
Statistician	Andrew Hedge, BSc, MSc
Medical Writer	Andrew Senior, BSc, PhD

A list of all co-investigators and associated curricula vitae are provided in [Appendix 16.1.4](#).

The signatures of the Principal Investigator, report authors, and the Sponsor signatories are provided in a separate document.



7 INTRODUCTION

Cigarette smoking causes pulmonary and cardiovascular diseases and other serious diseases in smokers [2]. The effects of smoking and smoking cessation on mortality from cardiovascular disease among the Japanese population were investigated in cohort studies in Japan. These studies confirmed the association between smoking and mortality from cardiovascular disease and highlighted the importance of smoking cessation at any age to prevent cardiovascular disease in the Japanese population [3, 4]. Despite the risks which are attributable to smoking, some smokers cannot refrain from smoking or decide to continue smoking.

More than 5,300 smoke constituents (the chemicals formed when tobacco is burned or combusted) have been identified [5], and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) [6]. For those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing candidate modified risk tobacco products (MRTPs) that provide an inhalation experience without combustion. The novel approach to achieve this is by heating tobacco at significantly lower temperatures than required for combustion of conventional cigarettes (CC). The Institute of Medicine observed that cessation is the “gold standard” for assessing risk reduction, and that “the closer risks and exposures from MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit” [7]. PMI utilizes smoking cessation/smoking abstinence as the benchmark for assessing the risk reduction potential of its candidate MRTPs.

The product developed by PMI, and that was assessed in this study, is the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for the combustion of CC, which can reach 900°C. The THS 2.2 is composed of the ‘THS Tobacco Stick Holder’, dedicated special Menthol Tobacco Sticks made of conventional tobacco, a Charger, and different accessories. The energy of the THS Tobacco Stick Holder is sufficient for approximately 6-minute session.

The non-clinical assessment of THS 2.2 Menthol and its predecessors are described in the IB [8] and supported the initiation of clinical studies. No new or increased toxicological hazard in the product’s aerosol was detected compared with CC smoke. The aerosol was chemically analyzed confirming that none of the determined HPHCs in the THS 2.2 Menthol were increased compared to the CC. The biological activity was tested in a number of *in vitro* assays to assess the cytotoxicity and genotoxicity of the aerosol fractions total particulate matter (TPM) and gas vapor phase (GVP). *In vitro* and *in vivo* results have corroborated that the absence of combustion when consuming tobacco substantially lowers toxic effects seen in these biological models. Further details on the clinical data are provided in the IB [8].



Several clinical studies have been conducted on THS 1.0 and THS 1.0 Menthol, an earlier development version of THS 2.2 Menthol, in Europe, Asia, Africa, and the United States. All studies showed reductions in exposure to the majority of measured HPHCs from both aerosol fractions, TPM and GVP, in subjects who used the THS 1.0 as compared to subjects continuing to smoke CC, both in controlled and ambulatory conditions. No clinical studies have been conducted with THS 2.2 Menthol.

The previous version of THS 2.2 Menthol, namely THS 2.1 (non-menthol version), was tested in 2 exploratory clinical studies to measure the plasma nicotine kinetic profile (www.clinicaltrials.gov identifier: NCT01780688) and to assess the reduction of exposure to HPHCs (www.clinicaltrials.gov identifier: NCT01780714) when switching from CC to THS 2.1. The observed plasma nicotine kinetic profile for THS 2.1 was similar to CC, and there were substantial reductions in the exposure to the majority of selected HPHCs. Clinical studies conducted so far have revealed no unexpected safety findings for any of the previous versions of THS 2.2 tested. Further details on the clinical data are provided in the IB [8].

The purpose of this clinical study was to compare the profile of nicotine uptake (rate and amount of nicotine absorbed) after single use of switching from menthol conventional cigarettes (mCC) to THS 2.2 Menthol and mCC in smoking Japanese healthy subjects. THS 2.2 Menthol was also compared with the nicotine replacement therapy (NRT) gum, used as a reference point.



8 STUDY OBJECTIVES

8.1 Primary Objective and Endpoints

The primary objective of this study was:

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

Endpoints:

Nicotine PK parameters (THS 2.2 Menthol vs. mCC):

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

8.2 Secondary Objectives and Endpoints

The secondary objectives of this study were:

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

Endpoints:

Primary nicotine PK parameters (THS 2.2 Menthol vs. NRT gum):

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

2. To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to infinity [$AUC_{(0-\infty)}$] and AUC from start of product use to the subject-specific time of maximum nicotine concentration following single use of the mCC or NRT gum product [$AUC_{(0-t^*)}$]) between the THS 2.2 Menthol and mCC, as well as the THS 2.2 Menthol and NRT gum.

Endpoints:

Secondary nicotine PK parameters:

- $AUC_{(0-\infty)}$.
- Partial $AUC_{(0-t^*)}$.

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

Endpoint:

- $t_{1/2}$.
5. To describe the differences on urge-to-smoke over time between the THS 2.2 Menthol and mCC, as well as between the THS 2.2 Menthol and NRT gum.

Endpoints:

Urge-to-smoke questionnaire (Questionnaire of Smoking Urges-brief [QSU-brief]):

- Total score
 - Factor 1
 - Factor 2
6. To describe product evaluation in the THS 2.2 Menthol and mCC users.

Endpoints:

Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]):

- 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 Menthol, as compared to mCC 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 Menthol malfunction/misuse.
- Respiratory symptoms: cough assessment by Visual Analogue Scale (VAS) and Likert scales and 1 open question.
- Vital signs.



- Spirometry.
- Electrocardiogram (ECG).
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medications.

8.3 Study Hypotheses and Evaluation Criteria

8.3.1 Hypotheses

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

For the secondary objectives the following hypotheses was examined for THS 2.2 Menthol versus NRT gum analysis:

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

8.3.2 Evaluation Criteria

The study was considered successful if the 95% confidence interval (CI) of the THS 2.2 Menthol:mCC ratio for the nicotine C_{\max} and $AUC_{(0-\text{last})}$ were estimated with a precision of $\pm 20\%$.



9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a randomized, controlled, 2-period, 4-sequence, single use crossover study with each subject using 2 of the following 3 products:

- THS 2.2 Menthol.
- mCC.
- NRT gum.

A Screening Visit was conducted within 4 weeks prior to Admission to the investigational site (Day -29 to Day -2) (Figure 1). A demonstration of the THS 2.2 Menthol and the NRT gum was performed by the site collaborator during the Screening Visit. Subjects returned to the site and were admitted to the clinic on Day -1.

On Day -1, as the last procedure of the eligibility assessments, all subjects performed a product test prior to enrollment: first THS 2.2 Menthol (using up to 3 Menthol Tobacco Sticks) and subsequently NRT gum. In female subjects, product tests with either the THS 2.2 Menthol or NRT gum were only performed after pregnancy had been excluded by a negative urine pregnancy test. Only subjects willing and ready to use both the THS 2.2 Menthol and the NRT gum products were enrolled in order to minimize the dropout rate during the course of the study.

The confinement period consisted of 2 periods (Period 1 and Period 2), with each period consisting of at least a 24-hour nicotine wash-out (nicotine abstinence) and 1 day of single product use.

Period 1: Day 0: Wash-out; Day 1: single product use (THS 2.2 Menthol/mCC/NRT gum).

Period 2: Day 2: Wash-out; Day 3: single product use (THS 2.2 Menthol/mCC/NRT gum).

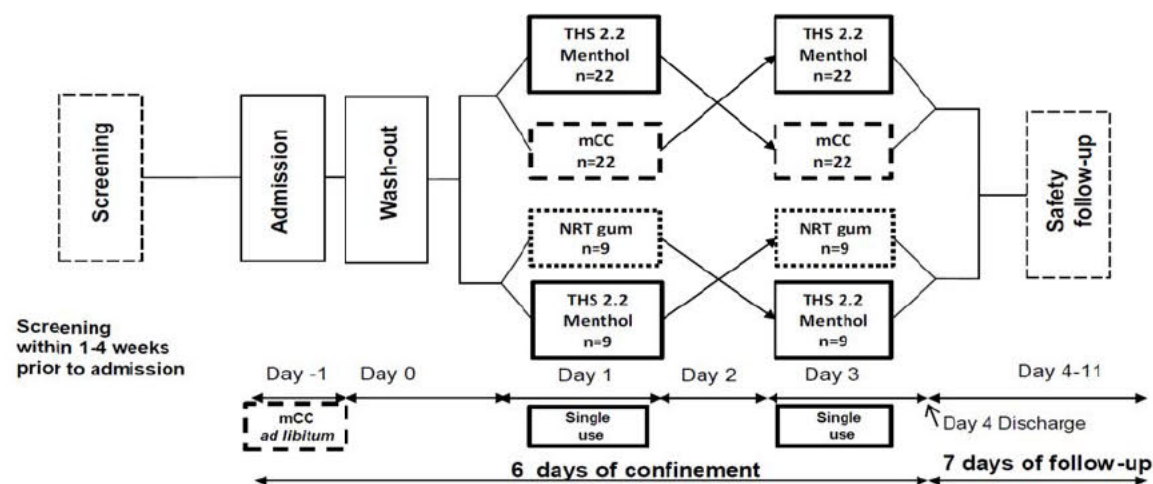
In total, 62 eligible, mCC-smoking subjects were randomized into 1 of the 4 sequences:

**Table 1 Definition of Randomization Groups and Sequences**

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

Abbreviations: mCC = menthol conventional cigarette; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Subjects were discharged from the investigational site in the morning of Day 4 following completion of all Day of Discharge examinations. After discharge there was a 7-day safety follow-up period to record spontaneously reported new AEs or SAEs, and for the site to actively follow-up on ongoing AEs/SAEs. End of Study was defined as the last day of the 7-day safety follow-up subsequent to discharge from the unit.

Figure 1 Study Flow Chart

Abbreviations: mCC = menthol conventional cigarette; N = number of subjects; NRT = nicotine replacement therapy; THS 2.2 = Tobacco Heating System 2.2.

The detailed study protocol and sample case report form (CRF) are provided in [Appendix 16.1.1](#) and [Appendix 16.1.2](#), respectively.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The minimum of 23 years of age was selected based on the legal age of smoking in Japan being 20 years old coupled with the requirement of 3 years of smoking history. Smokers



of mCC were assessed because the menthol brands play a significant role within the Japanese market, with 20% of the overall market share in 2008 [9].

In this study, mCC were used as a reference product and a market-approved pharmaceutical NRT gum 2 mg (Nicorette®) was used as non-investigational reference point. Despite the availability of mCC brand with International Organization for Standardization (ISO) nicotine level >1.0 mg in Japan, the maximum ISO nicotine level allowed was 1.0 mg because the percentage of the mCC brands >1.0 mg is low. The amount of nicotine and the rate of absorption following nicotine nasal spray (NNS) use are comparable to those obtained following CC use and are different to those resulting from chewing NRT gum. The NRT gum was selected for this study because NNS are not cleared for medical use in Japan.

The NRT gum served as a reference point for comparison with THS 2.2 Menthol for the following endpoints:

- Nicotine PK parameters.
- Urge-to-smoke.
- Safety profile.

The nicotine wash-out period was set to at least 24 hours ($>5 \times$ elimination $t_{1/2}$) as the elimination $t_{1/2}$ of nicotine in blood is around 2 hours in Caucasian smokers [10]. A longer wash-out (approximately 30 hours) was used for this study to account for the expected slower nicotine metabolism in the Japanese population.

The use of estrogen contraceptives is known to accelerate nicotine clearance by 20% to 30% in women as compared to women who do not take such contraceptives [11]. Therefore, for the purpose of this study, it was not permitted to use hormonal contraception containing estrogens. This also applied to hormone replacement therapy.

Furthermore, cytochrome P450 (CYP) 2A6 activity was assessed in this study. Asians on average metabolize nicotine more slowly than Caucasians do, at least in part due to a high prevalence of the CYP2A6 alleles associated with reduced or absent enzyme activity [12].

9.3 Selection of Study Population

Sixty-two healthy adult Japanese female or male subjects, who smoked at least 10 mCC per day, were randomized into this study. The maximum number of mCC that could be smoked was not limited. Subjects had a smoking history of at least 3 years of consecutive smoking prior to Screening. The smoking status of the subjects was verified based on a urine cotinine test (cotinine ≥ 200 ng/mL). Each sex and each of the smoking strata (ISO nicotine levels ≤ 0.6 mg and >0.6 mg to ≤ 1 mg) represented at least 40% of the total study population.



9.3.1 Inclusion Criteria

Each subject had to meet the following criteria to be eligible for the study:

1. Subject had signed the ICF and was able to understand the information provided in the Subject Information Sheet and ICF.
2. Subject was aged from 23 to 65 years (inclusive).
3. Subject was Japanese.
4. Subject was a smoking, healthy subject as judged by the Principal Investigator, based on all available assessments in the Screening period/Day of Admission (e.g., safety laboratory, spirometry [measured forced expiratory volume in 1 second {FEV₁}/measured forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV₁ >80% predicted value, and post-bronchodilator FVC >0.8], vital signs, physical examination, ECG, chest X-ray, and medical history).
5. Subject was smoking at least 10 commercially available mCC per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/mCC, as labeled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject had been smoking for at least the last 3 consecutive years. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
6. The subject did not plan to quit smoking in the next 3 months
7. The subject was willing and able to accept interruptions of smoking for up to 4 days.
8. The subject was willing and able to accept using both the THS 2.2 Menthol and NRT gum products.

9.3.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. As per Principal Investigator judgment, the subject could not participate in the study for any reason (e.g., medical, psychiatric, and/or social reason).
2. A subject who was legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners or subjects who were involuntarily incarcerated).
3. The subject had a medical condition that required smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease, or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Principal Investigator.
4. The subject had a body mass index (BMI) <18.5 or ≥32.0 kg/m².



5. As per Principal Investigator judgment, the subject had medical conditions which required, or in the course of the study would have required, a medical intervention (e.g., start of treatment, surgery, hospitalization) which could have interfered with the study participation and/or study results.
6. The subject had used nicotine-containing products, other than commercially available mCC (either tobacco-based products or NRT), as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
7. The subject had received medication (prescription or over-the-counter [OTC]) within 14 days or within 5 half-lives of the drug prior to the Admission Day (Day -1; whichever was longer) that had an impact on CYP2A6 activity.
8. If the subject had received any medication (prescribed or OTC) within 14 days prior to Screening or prior to the Admission Day (Day -1) it was at the discretion of the Principal Investigator to decide whether these could potentially interfere with the study objectives and subject's safety.
9. The subject had a positive alcohol test and/or the subject had a history of alcohol abuse that could interfere with subject's participation in study.
10. The subject had a positive urine drug test.
11. Positive serology test for human immunodeficiency virus (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 was a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
14. The subject was an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, child).
15. The subject had participated in a clinical study within 3 months prior to the Screening Visit.
16. The subject had previously participated in the same study at a different time (i.e., each subject could be included in the study population only once).

Additionally, women were excluded if:

17. The subject was pregnant (did not have negative pregnancy tests at Screening and at Admission) or was breast feeding.
18. The subject did 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 were not considered effective methods) from Screening until the end of the safety follow-up period. Hormonal contraception with estrogen-containing products was not allowed in this study.



9.3.3 Removal of Subjects from the Study

Subjects were informed that they were free to withdraw from the study at any time. Subjects were questioned for the reason of premature withdrawal, although they were not obliged to disclose it. Any details of withdrawals were fully documented in the source document and captured in the CRF.

If a subject had withdrawn or was removed from the study, the whole examination procedure planned for Day 4 was performed as soon as possible after the time of their discontinuation, unless the subject had withdrawn their informed consent to do so. After the time of discontinuation, the subject entered into the 7-day safety follow-up period. For the subject who decided to withdraw from the study (Subject 0107), the samples were analyzed until the time point of withdrawal following confirmation by the Principal Investigator that the subject still agreed to have their sample analyzed and data used.

Subjects had to be withdrawn from the study as a result of any of the following:

- Withdrawal of informed consent.
- Any AE or condition (including clinically relevant changes in a laboratory parameter), at the discretion of the Principal Investigator.
- Positive pregnancy testing (any invasive procedures, including the drawing of blood were prohibited after diagnosis of pregnancy)
- The Sponsor or Principal Investigator terminated the study. If the Sponsor or the Investigator decided to prematurely terminate the study, the head of the medical institution was promptly informed of the facts and reasons in writing.
- Withdrawal was considered to be in the best interest of the subject or the other subjects.

In addition, subjects could have been discontinued from the study for any of the following reasons:

- Lost to follow-up.
- Concomitant treatment with non-authorized medication as defined in the context of this study (in general, any concomitant medication was to be discussed with the (b) (4) Medical Monitor on an ongoing basis).
- If a subject used any CC or nicotine/tobacco-containing product other than the product/regimen he/she was assigned to, it was at the discretion of the Investigator to decide whether or not to withdraw the subject from the study.
- Non-compliance with the study procedures

Subjects withdrawn prematurely after randomization were not replaced and were not allowed to re-enter the study.



9.3.3.1 Violation of Selection Criteria

Subjects who were eligible at Screening, but who did not meet the entry criteria on Admission Day (Day -1) were considered a screening failure.

Subjects who violated the entry criteria prior to enrollment, but who were considered eligible, were to be immediately withdrawn from the study when the violation was detected.

9.4 Investigational Products

9.4.1 Investigational and Reference Cigarettes

9.4.1.1 THS 2.2 Menthol

The THS 2.2 Menthol was supplied by the Sponsor and comprised the following components: Menthol Tobacco Stick, Holder, Charger, and accessories (see Appendix 3 of the protocol [[Appendix 16.1.1](#)] for more information regarding the product user guide).

Charger:	The function of the Charger (Model 4) was to recharge the Holder after use. It contained a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around, and could be recharged from a main power source.
Tobacco Stick Holder (Holder):	The function of the Holder (Model 4.2) was to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating was powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Menthol Tobacco Stick)
THS Menthol Tobacco Stick (Menthol Tobacco Sticks):	The Menthol Tobacco Stick (product code C3 menthol) contained tobacco which, when heated, generated an aerosol. It was custom-designed to be used with the Holder.

The overall objective of the design was to provide an acceptable experience in which the HPHCs level in the aerosol was substantially reduced in comparison with mCC.

The pack batch number of the THS Tobacco Sticks was B-05775 and the production date was 12 June 2013, and the expiry date was 11 January 2014.

Device inventory data are listed in [Appendix 15, Listing 15.3.2.2](#).



9.4.1.2 Menthol Conventional Cigarettes

In study THS 2.2 Menthol – mCC and mCC – THS 2.2 Menthol sequences, the reference product to THS 2.2 Menthol was a commercially available single-brand mCC with a maximum ISO yield of 1 mg nicotine per cigarette.

Menthol CC were not provided by the Sponsor. All eligible subjects were asked to purchase their own preferred single-brand mCC prior to Admission. As randomization took place on Day 0, every study subject needed to buy his/her anticipated number of single-brand mCC for a total of 2 days, plus 2 extra packs.

9.4.2 Reference Point Products

Nicotine replacement therapy gum (Nicorette 2 mg gum) was the reference point product to THS 2.2 for THS 2.2 Menthol – NRT gum and NRT gum – THS 2.2 Menthol sequences. The NRT gum was supplied by the site, and the site was reimbursed by the Sponsor.

9.4.3 Packaging and Labeling

At Admission on Day -1, all study subjects provided their anticipated number of mCC (as outlined in [Section 9.4.1.2](#)) in sealed packs to the site collaborator. The cigarette packs provided by the subjects were unopened with the cellophane wrappers intact.

Each pack of cigarettes provided by the subject was labeled to identify which subject the cigarettes belonged to (labels were affixed to the cellophane wrapper of the lower part of the pack by the study site trial collaborator). Packs of mCC were labeled to identify necessary information to match the subject with his/her supply

For the THS Menthol Tobacco Sticks, the packs and cartons were pre-labeled with the necessary information including the product code. The labels were written in Japanese (see Appendix 4 of the protocol [[Appendix 16.1.1](#)]).

9.4.4 Storage and Accountability

The THS 2.2 Menthol, NRT gum, and mCC were stored in a secured site storage place with access limited to the authorized personnel only. Full accountability of the distributed products was ensured by the designated collaborator. Subjects returned the butt of any used THS Menthol Tobacco Stick or mCC immediately after use to the site study collaborator for accountability. Subjects also returned each used NRT gum after use to the site study collaborator. This was documented in appropriate log(s). At the time of discharge, unused mCC given to the site study collaborator at Admission on Day -1 were returned to the subjects.



9.4.5 Investigational Product/Reference Point Product Retention

Unused NRT gum was destroyed upon study completion. All unused THS Menthol Tobacco Sticks were returned to the Sponsor and destroyed. The Tobacco Heating Devices, including all components and accessories, were returned to the Sponsor.

9.4.6 Method of Assigning Subjects to Study Arms

Randomization to product exposure sequence was done through an Interactive Telephone and Web Response System. Each sex and each smoking level (ISO nicotine levels ≤ 0.6 mg and >0.6 mg to ≤ 1 mg) had a quota applied to ensure they represented at least 40% of the total study population allocated within the Group-1 and Group-2 populations (Table 1).

In particular, the maximum number of subjects of the same sex or nicotine level value was limited to 26 in Group-1 and 10 in Group-2.

The randomization of the planned sample size of 62 subjects was ensured by applying a quota to the number of subjects per each sequence (22 subjects for sequences in Group-1, and 9 subjects for sequences in Group-2).

The subject randomization list contained randomized records for the 2 groups. An incomplete block design was used for randomization, with blocks of size 6. Subjects were assigned to the next available sequence providing the quotas had not been met. Other randomization details were detailed in the randomization plan.

The randomization scheme was generated by the statistical division within (b) (4) and none of the Sponsor and (b) (4) collaborator, Investigator, or study subjects had access to the randomization schema prior to randomization. The randomization sequence and codes are provided in Appendix 16.1.6.

9.4.7 Administration of Investigational/Reference Point Products

Subjects were never requested or forced to smoke and were free to stop smoking at any time during the study. Subjects caught using any nicotine/tobacco product which was different from the assigned product on a given day were withdrawn from the study.

During the Screening period, subjects were allowed to smoke according to their normal smoking habits except during the procedures of the Screening Visit at the discretion of the site.



9.4.7.1 Admission Day (Day -1)

Subjects were instructed not to smoke in the morning prior to Admission. Smoking *ad libitum* was allowed throughout the Day of Admission, except during procedures, until 11:00 PM. All subjects were allowed to continue smoking their preferred mCC *ad libitum*.

All subjects underwent a THS 2.2 Menthol test first (using up to 3 Menthol Tobacco Sticks) and subsequently, NRT gum test at Day -1 prior to enrollment. Each subject slowly chewed the 2 mg NRT gum for 35 ± 5 minutes while spacing each chew, leading to an administered dose of 1 mg nicotine/product use as per label similarly to the day of single use.

Following agreement that the subjects were willing to use THS 2.2 Menthol and NRT gum, subjects were enrolled.

9.4.7.2 Investigational Period (Day 0 to Day 3)

During the first wash-out, each subject maintained nicotine abstinence from Day -1 at 11:00 PM to the time of single use of his/her allocated product at Day 1 (approximately 33 to 38 hours wash-out). At Day 1, after the single use of the product, subjects maintained nicotine abstinence for the rest of the day. During the second wash-out on Day 2, subjects maintained nicotine abstinence until the time of single use of subject's allocated product at Day 3 (approximately 47 to 49 hours wash-out). Subjects were not allowed to smoke or use any other nicotine/tobacco-containing products other than the product/regimen they were allocated to.

Time point of first product use during study day (T_0) was defined as start of the single product use at the single use days. The start time of the use of each product was documented on single use days (Day 1 and Day 3). The start of product use for THS 2.2 Menthol was defined as the time of the first puff. The start time for mCC corresponded to the lighting of the mCC, and the start time of the NRT gum was the time of the NRT gum intake. The 30 seconds it took to pre-heat the Holder were not taken into account.

For NRT gum, the start time and the stop time were documented in the appropriate log.

The start of the first product use could have been different for each subject for both days of product use; however, the product use had to be in the window of 06:00 AM to 09:00 AM. During the study, no subject used their allocated product outside the time window defined by the protocol.

Single Use of Products (Day 1 and Day 3)

On Day 1 and Day 3, subjects used the product they were randomized to only once in the morning between 06:00 AM to 09:00 AM, and abstained from usage of the product or other nicotine/tobacco-containing items for the rest of the day, i.e., subjects in the THS 2.2 Menthol arm used 1 THS Menthol Tobacco Stick, subjects in the mCC arm smoked 1 mCC, and subjects in the NRT gum arm chewed 1 piece of 2 mg NRT gum 35 \pm 5 minutes while spacing each chew in accordance with the product label, leading to an administered dose of 1 mg nicotine per product use.

Table 2 Product Assignment on Single Use Days

	Sequence 1	Sequence 2	Sequence 3	Sequence 4
Day 1	THS 2.2 Menthol	mCC	THS 2.2 Menthol	NRT gum
Day 3	mCC	THS 2.2 Menthol	NRT gum	THS 2.2 Menthol

Abbreviations: mCC = menthol conventional cigarette; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

9.4.7.3 Day of Discharge/Time of Discharge

On the Day of Discharge (Day 4), smoking was only allowed after all laboratory procedures and spirometry assessments had been performed. All examinations on the Day of Discharge were conducted on Day 4 prior to the time of Discharge. Subjects who withdrew from the study underwent the Day of Discharge procedures as soon as possible and entered the period of safety follow-up.

9.4.7.4 Safety Period

During the safety follow-up period, subjects were free to smoke according to their usual smoking habits.

9.4.8 Smoking Stopping Rules for Smokers

For safety purposes, smoking of the THS 2.2 Menthol or the mCC, or the use of NRT gum was to be temporarily stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach, or abdominal pain), cold sweats, headache, dizziness and breathing problems, or any other reason at the discretion of the Principal Investigator.

9.4.9 Selection and Timing of Investigational Product Use for Each Subject

Subjects did not have free access to the THS 2.2 Menthol (including the THS Menthol Tobacco Sticks), the mCC, or the NRT gum during the confinement period. The investigational product (IP) and reference products were stored and dispensed by the



Principal Investigator or designated study site collaborator, one at a time, as described in [Section 9.4.4](#). The timing of THS 2.2 Menthol Tobacco Sticks, mCC, or the NRT gum use was as described in [Section 9.4.7.2](#).

9.4.10 Blinding/ Unblinding

This was an open-label study; therefore the subjects and Principal Investigator were unblinded to subjects' sequence. However, there was a limited degree of blinding in the data review and data analysis process. In particular, PMI and Covance personnel were blinded to the randomization sequence as summarized in [Table 3](#).

Table 3 Blinding Scheme

Blinded Study Personnel	End of Blinding Period
PMI and Covance study statisticians	After the database lock.
PMI data manager	After the finalization of PMI blind database review.
PMI safety and clinical scientist	After the finalization of PMI blind database review.

A Covance PK expert performed an unblinded data review of PK data and flagged any anomalous data for the pre-analysis blinded data review conducted by PMI and Covance.

As part of the PMI Quality Control (QC) activity, data listings were reviewed by Covance and PMI before database lock, with no access to the randomization sequence information. Full details including the definition of the blinded and unblinded PMI study teams are available in the data review plan (Version 1.1 date: 22-April-2014).

9.4.11 Prior and Concomitant Therapy

Subjects were not permitted to take any concomitant medication during this study. Any medication with an impact on the CYP2A6 metabolism (prescription or OTC products) had to be avoided because CYP2A6 is involved in nicotine metabolism.

The use of hormonal contraceptives or hormone replacement therapy containing estrogens was not allowed in this study. However, the use of hormonal contraceptive products containing progesterone only was allowed. No subjects were withdrawn for having used estrogen during the study.

[Table 4](#) shows drugs and substances that are considered as having an impact on CYP2A6 activity [13]. Prior to database lock, concomitant medication was assessed for its potential impact on CYP2A6 activity and potential impact on study results. No subjects reported the use of prior medication and no subjects received concomitant medication during the study ([Appendix 15, Listings 15.3.6.3.1 and 15.3.6.3.2](#)).

**Table 4 CYP2A6: Substrates, Inhibitors, and Inducers**

Inhibitor	Drug Class
Amiodarone	Antiarrhythmic agent, Class III
Desipramine	Antidepressant
Isoniazid	Anti-bacterial drug
Ketoconazole	Anti-fungal medication
Letrozole	Anti-estrogen drug
Methoxsalen	Systemic psoralens
Miconazole	Anti-fungal medication
Tranylcypromine	Antidepressant
Inducer	Drug Class
Amobarbital	Barbiturate
Pentobarbital	Barbiturates
Phenobarbital	Barbiturates/anticonvulsa
Rifampin	Antimycobacterials
Secobarbital	Barbiturates
Substrate	Drug Class
Dexmedetomidine	α_2 -Adrenoceptor, sedative
Ifosfamide	Anti-cancer, alkylating agents

Data source: Drug Information Handbook, 2014 [13]

The Principal Investigator was responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescription of medication were taken in the best interest of the subject.

The use of any concomitant medication that could not be avoided for safety reasons were fully documented and followed up with the (b) (4). Clinical Research's Medical Monitor on an ongoing basis.

Concomitant medications were first assessed at the Screening Visit. For subjects to be eligible for the study, any medication with impact on CYP2A6 metabolism must have been discontinued at least 14 days or 5 half-lives (whichever was longer) prior to the subject's admission to the study.

Furthermore, concomitant medications were not to be used during the entire study until the time of discharge, but were allowed during the safety follow-up. It was at the discretion of the Principal Investigator to assess whether termination of such medications at Screening was medically justified and safe for the subject.



9.4.12 Compliance to Investigational Product

Compliance for all arms was ensured by strict distribution of the products (product by product), and collection of used THS Menthol Tobacco Sticks, the mCC butts, and the NRT gum was documented in appropriate logs.

In addition, for subjects using NRT gum, the compliance was chemically verified by exhaled CO breath. The cut-off point for the CO breath test value to distinguish tobacco use versus no tobacco use was 10 ppm [14].

Furthermore, the CO breath test was considered as one of the measures of compliance during wash-out days in all subjects.

9.4.13 Subject Restrictions

In general, concomitant medications were not permitted during this study (see [Section 9.4.11](#)). In addition to the restrictions described in the inclusion and exclusion criteria (see [Sections 9.3.1](#) and [9.3.2](#)), the following smoking and dietary restrictions applied to subjects in this study. The smoking and dietary restrictions applied to subjects in this study are described in [Section 9.4.13.1](#) and [Section 9.4.13.2](#), respectively.

9.4.13.1 Smoking Restrictions

On Day 1 and Day 3, to avoid nicotine cross-contamination, users of THS 2.2 Menthol and smokers of mCC used or smoked, as applicable, in dedicated separate rooms: 1 room for THS 2.2 Menthol and 1 room for mCC. Each individual subject used their THS 2.2 Menthol or mCC alone in a room dedicated to the product, with an interval between subjects to allow ventilation of the room. Subjects receiving NRT gum did not have access to these rooms.

In the morning prior to Admission, subjects were instructed not to smoke. At Admission, smoking was only allowed during the designated smoking times (06:30 AM to 11:00 PM) as detailed in the study design. Subjects did not have free access to their NRT gum, mCC, or THS 2.2 Menthol, which were dispensed by the study site collaborator individually as described in [Section 9.4.4](#).

Smoking was not allowed during study procedures except during blood sampling for nicotine PK on Day 1 and Day 3. Furthermore, smoking was not allowed on Day 4 until all laboratory tests and spirometry assessments had been conducted.

During the days of wash-out or single product use (for mCC and THS 2.2 Menthol arms), no NRT gum or other products supportive to smoking abstinence were used or were provided to the subjects.



9.4.13.2 Dietary Restrictions

A standard diet was designed by a dietician for the whole confinement period. For each meal, the caloric and fat content was controlled in order to avoid a “high-fat” diet. The Food and Drug Administration (FDA) guidance on food-effect studies for bioequivalency testing identifies a “high-fat” diet as a diet in which fat comprises approximately 50% of total caloric content of the meal and is high in calories (approximately 800 to 1000 calories) [15].

Subjects were not allowed to bring their own food or beverages to the investigational site. Meals were served according to the schedules provided in Section 9 of the protocol ([Appendix 16.1.1](#)). Additional light snacks, fruits, and raw vegetables could be distributed to the subjects without restrictions at any time during confinement as long as they fulfilled the above requirements described in this section.

Consumption of water was allowed as desired. The same menu and meal schedule was administered uniformly for all subjects in all study arms.

Subjects fasted for at least 10 hours prior to blood draws for the safety laboratory at the Screening Visit, on Day -1, and Day 4.

9.5 Study Variables Assessed and Schedule of Events

All study site collaborators who conducted the study measurements or recording had appropriate training. Quality Control (QC) measures were in place. All study procedures are provided as an overview in the Schedule of Events ([Table 6](#) in [Section 9.5.8](#)).

Not all subjects could have a study assessment/procedure at exactly the same time; therefore, adequate time windows were permitted for each study procedure and time point (see Section 9 of the protocol [[Appendix 16.1.1](#)] and Section 6.1 of the SAP [[Appendix 16.1.8](#)]). Study site collaborators adhered to the site’s Standard Operating Procedures (SOPs) for all activities relevant to the quality of the study.

9.5.1 Pharmacokinetic Assessments

The primary PK endpoint variables for this study were the nicotine PK parameters (THS 2.2 Menthol vs. mCC), as assessed by:

- C_{\max} .
- $AUC_{0-\text{last}}$.

The secondary PK endpoint endpoints for this study were:

- Primary PK parameters of nicotine (THS 2.2 Menthol vs. NRT gum).



- Secondary nicotine PK parameters:
 - $AUC_{(0-\infty)}$.
 - Partial $AUC_{(0-t^*)}$.
 - t_{max} .
 - $t_{1/2}$.

9.5.2 Other Secondary Assessments

- Subjective smoking effects:
 - Urge-to-smoke questionnaire (QSU-brief).
 - Product evaluation questionnaire MCEQ).
- CO exposure biomarkers: levels of exhaled CO and COHb in blood.

9.5.3 Safety Variables and Measurements

Safety variables were assessed in this study at the time points shown in [Table 6](#) and included: AEs (including device malfunction or misuse), SAEs, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), ECG data, spirometry, clinical laboratory safety panel (hematology, clinical chemistry, and urine analysis), concomitant medication, physical examination (including BMI), and respiratory symptoms (cough assessment).

9.5.3.1 Adverse Events

An AE was defined as any untoward medical occurrence in a subject, or clinical investigation subject administered an IP including tobacco products [\[16\]](#), which did not necessarily have a causal relationship with the IP or reference point product. An AE could therefore have been any unfavorable and unintended sign (including a clinically relevant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP or reference point product, whether or not related to the IP or reference point product.

Full details of the definitions of AEs and the procedures related to them are provided in the protocol ([Appendix 16.1.1](#))

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

- Resulted in death.
- Was life threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.



- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect.

Important medical events that did not result in death, were not life-threatening or did not require hospitalization were to be considered as an SAE when, based on appropriate medical judgment, they jeopardized the subject or the subject required medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

Any pre-planned hospitalizations that were known at the time of signing the ICF were not to be recorded as SAEs (they were to be recorded only as AEs). Any AE that occurred during this pre-planned hospitalization was considered according to the above definitions.

The definitions of an SAE, the procedures for reporting of SAE, and for notifying the relevant IRB are provided in Sections 8.1 and 8.3 of the protocol ([Appendix 16.1.1](#)).

The Principal Investigator was responsible for obtaining, assessing, and documenting all AEs during the study. Adverse event information was collected via spontaneous reporting or elicited by the use of consistent, open, non-directive questions from study site collaborator (e.g., “Have you had any health problems since the previous visit/how are you feeling since you were last asked?”). At the discretion of the Principal Investigator, the collection of AE information could be triggered from his/her review of the subject questionnaires and the VAS. However, the main source for AE collection was the face-to-face interview with the subject.

Full details of the AE information recorded and period of collection are provided in the protocol ([Appendix 16.1.1](#))

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

- Mild: The AE was easily tolerated, no interference with activities of daily living (ADL)
- Moderate: The AE interfered with ADL, but subject was still able to function
- Severe: The AE was incapacitating and required medical intervention

All AEs were assessed by the Investigator and categorized as ‘related’ or ‘not related’ to IP, reference point products, or study procedures according to the following definitions:

- Not related: The temporal relationship of the clinical event to a study product administration or a study procedure made a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provided a sufficient explanation for the observed event.



- **Related:** The temporal relationship of the clinical event to a study product administration or a certain study procedure made a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions did not provide a sufficient explanation for the observed event.

An AE was regarded as ‘unexpected’ if its nature or severity was not consistent with information already known about the IP or reference product, and/or had not been previously observed and was not listed in the current IB. The IB provides further detail on signs or symptoms that might be expected with the use of the IP, including information relating to device malfunction or misuse.

Full details of the assessment of AE intensity and relationship to IP, reference point product, or to the study procedures, and of the expectedness of an AE, are provided in Sections 8.2.3, 8.2.4, and 8.2.5 of the protocol ([Appendix 16.1.1](#)).

Details of reporting of other events critical to safety evaluations (including abnormal laboratory tests) are provided in Section 8.4 of the protocol ([Appendix 16.1.1](#)).

Details of the reporting of pregnancies and AEs leading to withdrawal are provided in Section 8.5 of the protocol ([Appendix 16.1.1](#)).

9.5.3.2 Physical Examination

A physical examination was conducted at the Screening Visit, at Admission (Day -1), and on the Day of Discharge (Day 4). Body weight was recorded at the same time points. Body height was measured only at the Screening Visit. The BMI was calculated from the body weight and height using the following formula:

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

9.5.3.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate were measured at the Screening Visit, at Admission (Day -1), and on every day of confinement (Day 0 to Day 4). All parameters were recorded after the subject had rested for at least 5 minutes in a supine position.

For each measurement, it was documented, as a deviation, whether the subject had smoked within 15 minutes prior to the measurement.



9.5.3.4 Clinical Laboratory Parameters

Hematology, clinical chemistry, and urine analysis for the safety panel were measured at Screening, on the Day of Admission (Day -1), and on the Day of Discharge (Day 4), irrespective of product use. Laboratory safety tests were conducted at a local laboratory. Blood was collected from the subject after at least 10 hours of fasting (see [Section 9.4.13.2](#)). The urine test was performed semi-quantitatively as a urine dipstick test at the site. The parameters measured are listed in [Table 5](#).

Table 5 Clinical Laboratory Parameters for Safety Panel

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	Red blood cell traces
Mean corpuscular volume	Blood urea nitrogen	Protein
Platelet count	Creatinine	Specific gravity
Red blood cell count	Gamma-glutamyl transferase	
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	

9.5.3.5 Electrocardiogram

A standard 12-lead ECG was recorded at Screening, and post-product use on Day 1 and Day 3. The ECG testing was performed as per the site's local practice and was recorded after the subject had rested for at least 10 minutes in a supine position.

The following parameters were documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected by the ECG device according to Bazett's formula. Every ECG was assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis was provided in the CRF for all ECGs assessed as abnormal – clinically relevant. Print-outs of ECGs were interpreted by a qualified physician. Any printouts of ECGs on thermosensitive paper were photocopied, initialed, dated, and stapled together for inclusion in the Source Data File.



9.5.3.6 Urine Drug Screen

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

9.5.3.7 Breath Alcohol Test

Subjects had a breath alcohol test at the Screening Visit and on the Day of Admission, using an alcometer device.

9.5.3.8 Medical History and Previous Medications

Relevant medical history and any concomitant diseases were documented at the Screening Visit. Medical history was defined as any condition that started and ended prior to Screening. A concomitant disease was defined as any condition that started prior to the Screening Visit and was still ongoing at the Screening Visit.

Any clinically relevant findings detected during the Screening Visit were documented as concomitant disease.

Prior medication taken within 4 weeks prior to Screening Visit and any concomitant medication was documented. Any medication started prior to the Screening Visit and was still being taken by the subject was considered a concomitant medication. Medication initiated after Screening was also referred to as concomitant medication.

9.5.3.9 Urine Pregnancy Tests

All female subjects underwent pregnancy testing at the Screening Visit, on the Day of Admission, and on the Day of Discharge (Day 4). Female subjects with a positive pregnancy test at the Screening Visit or on Day -1 were not to be enrolled and were to be considered a screening failure. Any pregnancy in such subjects was not to be followed up as no exposure to the THS 2.2 Menthol would have occurred. The product test at Admission was to be performed only in female subjects with a negative pregnancy test. In any case of a positive pregnancy test, the Principal Investigator was to inform the subject about the risks associated with smoking during pregnancy. In the event of unclear urine pregnancy test, the absence of pregnancy was to be confirmed by a serum follicle stimulating hormone level >20 IU/l.

All pregnancies detected during the study were to be reported and handled as described in Section 8.5.1 of the protocol ([Appendix 16.1.1](#)).



9.5.3.10 Serological Tests

A test for hepatitis B surface antigen, hepatitis C virus, and HIV (anti-HIV1/2 and p24 antigen) was performed at Screening.

9.5.4 Other Clinical Assessments

9.5.4.1 Urine Cotinine Screening Test

A urine dipstick cotinine test was performed at Screening and on the Day of Admission in order to confirm the subject's smoking status. The test detected cotinine at a level of ≥ 200 ng/mL, indicating that the subject was a smoker.

9.5.4.2 Chest X-ray

A chest X-ray (anterior-posterior and left lateral views) was assessed during the Screening period to exclude subjects with relevant pulmonary diseases. Subjects were referred to a radiology facility for this procedure. No new examination was required if the subject presented a chest X-ray with anterior-posterior and left lateral views at the Screening Visit which was not older than 6 months.

9.5.4.3 Spirometry

Spirometry, with and without a short-acting bronchodilator, was performed at the Screening Visit to evaluate inclusion/exclusion criteria (using the post-bronchodilator results). Spirometry without a bronchodilator was performed first, followed by spirometry with a bronchodilator.

Furthermore, spirometry without a bronchodilator was also performed on Day -1 (baseline values) and on Day 4 (for comparison with the baseline values). Spirometry was performed prior to smoking the first cigarette of the day.

All study site collaborators that performed lung function testing were appropriately trained. Quality control measures as required by the site quality management system were put in place and were properly documented and filed. The subject was submitted to a spirometry assessment with maximum voluntary ventilation measurement and the FEV₁ and FVC were recorded.

The assessed spirometry parameters included FEV₁, FVC, and FEV₁/FVC.

9.5.4.4 Demographic Data

Demographic data (sex, date of birth/age) were recorded at the Screening Visit.



9.5.4.5 Identification of the Current Cigarette Brand

Identification of the current mCC brand(s) smoked by the subject was done at the Screening Visit and at Admission. At the Screening Visit, smokers were asked to bring a pack of their current mCC brand(s) to the site. The site study collaborator documented the brand name and yields.

At Admission, subjects handed their mCC supply for the entire confinement period to the study site who took a photograph of the front and the side (bearing the tar and nicotine yields) of the cigarette packages supplied by the subject and documented the brand name and yields. Photographs were considered as source documentation. Copies of the photographs were provided to, and received by, the Sponsor on Compact Discs.

9.5.5 Bioanalytical Methods

All bioanalytical assays and laboratory assessments were carried out using validated methods. The bioanalytical methods used, and the results obtained were documented in the Bioanalytical Report ([Appendix 16.1.9](#)).

Details of the analytical laboratories used are shown in [Section 6](#).

9.5.6 Sample Collection, Storage, and Shipping

All blood samples were tested at Celerion with the exception of COHb blood samples and the safety laboratory samples, which were tested at (b) (4) and Tokiwa local laboratories in Japan, respectively (see [Section 6](#)). The urine dipstick for the safety laboratory tests, urine drug screen, urine pregnancy tests, and urine cotinine tests were performed by the site study collaborator. The tests were provided by the sites.

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

Detailed procedures for handling of samples are described in the separate sample handling manual. Details relating to destruction of samples are provided in [Section 7.7](#) of the protocol ([Appendix 16.1.1](#)).

9.5.6.1 Blood Samples

Blood samples were collected by qualified and trained site collaborators. Subjects were in a seated position during blood collection. The maximum total volume of blood drawn for each subject was around 190 mL.



9.5.6.2 Urine Samples

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

9.5.7 Other Study Procedures

9.5.7.1 Questionnaires

Questionnaires were used to assess the subjective effects of urge-to-smoke, product evaluation, nicotine dependence, and assessment of cough.

All questionnaires used in this study and the VAS were entered by the subject directly in the electronic patient reported outcomes (ePRO) device or completed on paper.

Symptoms or worsening of symptoms as documented on any of the questionnaires or the VAS were to be documented as AEs at the discretion of the Principal Investigator (see [Section 9.5.3.1](#)).

Copies of the questionnaires used are provided in [Appendix 16.1.2](#).

9.5.7.1.1 Fagerström Test for Nicotine Dependence (Revised Version)

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

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

9.5.7.1.2 Assessment of Cough

Subjects were asked if they had experienced a regular need to cough e.g., coughing several times in the last 24 hours prior to assessment. If the answer was 'Yes', the subject was asked to complete a VAS, 3 Likert scales, and an open question which also assessed the previous 24 hours. The questionnaire was conducted prior to product use.

The VAS assessed how bothersome the cough was to the subject, ranging from 'not bothering me at all' to 'extremely bothersome'.

Subjective intensity and frequency of cough, and the amount of sputum produced were assessed using the following Likert scales:



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

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

The assessment of cough was done on a daily basis from Day 0 to Day 4. On Day 2 and Day 4, questionnaires were asked 24 hours after T₀ of Day 1 and Day 3, respectively.

9.5.7.1.3 Modified Cigarette Evaluation Questionnaire

Product evaluation was assessed using the MCEQ [19]. The MCEQ assessed the degree to which subjects experienced the reinforcing effects of smoking, by measuring:

- Smoking satisfaction (satisfying, tastes good, enjoy smoking).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nauseous).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

This questionnaire was only completed by subjects who used the THS 2.2 Menthol or smoked mCC in the THS 2.2 Menthol – mCC and mCC – THS 2.2 Menthol sequences. The MCEQ was completed by the subject himself/herself on Day 1 and Day 3.

9.5.7.1.4 Questionnaire of Smoking Urges-brief

The subject's urge-to-smoke was assessed using the QSU-brief [20]. The QSU-brief is a self-reported questionnaire with 10 items to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicate a higher urge-to-smoke. The brief version is consistent with the expressions of craving found in the 32-item version of the QSU [21]. The questionnaire supports a multi-dimensional conceptualization of craving to smoke and demonstrated the utility of a brief multi-dimensional measure of craving [20].

All subjects in this study completed the QSU-brief by himself/herself at single-use study days as follows:



- THS 2.2 Menthol and mCC use:

The first assessment was done within 15 minutes prior to the start of product use (T_0). All other assessments were done thereafter in relation to T_0 : 15 minutes, 30 minutes, 45 minutes, 60 minutes, 2 hours, 4 hours, 6 hours, 9 hours, and 12 hours after T_0 .

- NRT gum use:

The first assessment was done within 15 minutes prior to the start of product use (T_0). All other assessments were done thereafter in relation to T_0 : 20 minutes, 30 minutes, 45 minutes, 60 minutes, 2 hours, 4 hours, 6 hours, 9 hours, and 12 hours after T_0 .

9.5.7.2 Biomarker Assessments

Carboxyhemoglobin measured in blood and exhaled CO were investigated as a measure of exposure to CO. The CO breath test also served to monitor compliance during the following study days:

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

9.5.7.2.1 Carbon Monoxide Breath Test

Concentration of CO in exhaled breath was measured using the same device (Micro+™ Smokerlyzer) for all study subjects. The test was performed for all subjects, including those using NRT gum.

Single CO breath tests were conducted on Day -1 and Day 4.

On Day 0, Day 1, Day 2, and Day 3, four CO breath tests were performed per day. On Day 1 and Day 3, the first test per day was performed ≤ 15 minutes prior to T_0 . On the wash-out days (Day 0 and Day 2), the first test was conducted between 08:00 AM and 09:30 AM. The 3 other tests on each day were conducted between 12:00 PM and 01:30 PM, 04:00 PM and 05:30 PM; and 08:00 PM and 09:30 PM.

Values >10 ppm were considered as non-compliant if such values were observed prior to first product use on the single use days for all exposures and throughout the single-use days for NRT gum exposures. During wash-out days values >10 ppm were considered non-compliant on Day 2 but were expected on Day 0 because smoking was *ad libitum* during Day -1.



9.5.7.2.2 Carboxyhemoglobin

Blood samples for COHb were taken as follows on Day 1 and Day 3:

A total of 5 blood samples were taken. The first sample was taken within 15 minutes prior to using the first product (T_0). Thereafter, the sampling times in relation to T_0 were at 15 minutes, 60 minutes, 4 hours, and 12 hours post- T_0 .

9.5.7.2.3 Biomarkers of Exposure to Nicotine

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

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

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

A total of 16 blood samples were taken for a 24-hour profile. The first blood sample was taken within 15 minutes prior to the single use (T_0'). Times of sampling are thereafter in relation to T_0' : T_1' after 10 minutes, T_2' after 20 minutes, T_3' after 25 minutes, T_4' after 30 minutes, T_5' after 35 minutes, T_6' after 40 minutes, T_7' after 45 minutes, T_8' after 60 minutes, T_9' after 2 hours, T_{10}' after 3 hours, T_{11}' after 4 hours, T_{12}' after 6 hours, T_{13}' after 9 hours, T_{14}' after 12 hours, and T_{15}' after 24 hours (this sample was drawn during the day following product use; i.e., wash-out).

9.5.7.2.4 Cytochrome P450 2A6 Activity

Cytochrome P450 2A6 activity was calculated as metabolic ratio of *trans*-3'-hydroxycotinine and cotinine measured on Day -1, as described in [Section 9.7.1.4.1](#).

9.5.8 Schedule of Events

[Table 6](#) presents the schedule of events for the entire study period.

**Table 6 Schedule of Events**

	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	•	•						
Enrollment		•						
Randomization			•					
Product demonstration of THS 2.2 Menthol and NRT gum	•							
Product test for THS 2.2 Menthol and NRT gum		•						
Product use				•		•		
Support during periods of reduced smoking/smoking abstinence (as required)			•	•	•	•		
Identification of current mCC brand	•	•						
Smoking history	•	•						
Readiness to abstain from smoking for up to 4 days	•	•						


Table 6 Schedule of Events (continued)

	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
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: Hematology, clinical chemistry, urine analysis	•	•					•	
B: Serology	•							
U: Urine drug screen, urine cotinine screen	•	•						
Alcohol test	•	•						
U: Pregnancy test (all females)	•	•					•	


Table 6 Schedule of Events (continued)

	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, mCC butts and NRT gum				•		•		
B: Plasma nicotine ^f				•	•	•	•	
B: COHb ^g				• (5x)		• (5x)		
CO breath test ^h		• (1x)	• (4x)	• (4x)	• (4x)	• (4x)	• (1x)	
B: <i>trans</i> -3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma		•						
FTND questionnaire	•							
QSU-brief questionnaire ⁱ				•		•		
MCEQ (modified version, only after THS 2.2 Menthol and mCC use)				•		•		
Cough assessment ^j			•	•	•	•	•	
AE/SAE recording	•	•	•	•	•	•	•	•

Abbreviations: AE = adverse event; BMI = body mass index; mCC = menthol conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450; 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-brief; SAE = serious adverse event; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol

B: Blood sample required.



U: Urine sample required.

- ^a Sex, date of birth/age.
- ^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 were taken as follows:

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

For subjects on THS 2.2 Menthol or on mCC, a total of 16 blood samples were taken for a 24-hour profile (Day 1 and Day 3). The first blood sample was taken within 15 minutes prior to the product use (T_0). Times of sampling were thereafter in relation to T_0 : T_1 after 2 minutes + 1 minute, T_2 after 4 minutes + 1 minute, T_3 after 6 minutes + 1 minute, T_4 after 8 minutes + 1 minute, T_5 after 10 minutes + 1 minute, T_6 after 15 minutes + 2 minutes, T_7 after 30 minutes + 2 minutes, T_8 after 45 minutes + 2 minutes, T_9 after 60 minutes + 3 minutes, T_{10} after 2 hours + 5 minutes, T_{11} after 4 hours + 5 minutes, T_{12} after 6 hours + 5 minutes, T_{13} after 9 hours + 5 minutes, T_{14} after 12 hours + 5 minutes, and T_{15} after 24 hours + 5 minutes (this sample was 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 were taken for a 24-hour profile (Day 1 and Day 3). The first blood sample was taken within 15 minutes prior to T_0 . Thereafter in relation to T_0 : T_1 after 10 minutes + 1 minute, T_2 after 20 minutes + 1 minute, T_3 after 25 minutes + 1 minute, T_4 after 30 minutes + 1 minute, T_5 after 35 minutes + 1 minute, T_6 after 40 minutes + 1 minute, T_7 after 45 minutes + 1 minute, T_8 after 60 minutes + 3 minutes, T_9 after 2 hours + 5 minutes, T_{10} after 3 hours + 5 minutes, T_{11} after 4 hours + 5 minutes, T_{12} after 6 hours + 5 minutes, T_{13} after 9 hours + 5 minutes, T_{14} after 12 hours + 5 minutes, and T_{15} after 24 hours + 5 minutes (this sample was drawn during the day following product use, i.e., wash-out).

- ^g COHb blood samples were taken as follows:

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

- ^h A CO breath test was conducted once on Day -1 and Day 4. On Day 0, Day 1, Day 2, Day 3, four breath tests were done per day. On Day 1 and Day 3, the first test per day was performed within 15 minutes prior to T_0 (T_0 = start of first product use) the 3 other tests were conducted at 12:00 PM to 01:30 PM, 04:00 PM to 05:30 PM, and 08:00 PM to 09:30 PM. On the wash-out days (Day 0 and Day 2), the first test was conducted between 08:00 AM to 09:30 AM, the 3 other tests were conducted at 12:00 PM to 01:30 PM, 04:00 PM to 05:30 PM, and 08:00 PM to 09:30 PM.

- ⁱ QSU-brief was assessed as follows:

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

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



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

- ^j Visual analogue scale, 3 Likert scales and 1 open question.
- ^k All examinations listed at the Day of Discharge were 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.



9.5.9 Appropriateness of Measurements

The measurement of the PK, biomarkers of exposure, questionnaires, and safety variables allowed the objectives of this study to be addressed.

All laboratory measures used for this study were validated and were appropriate for the study assessments.

All questionnaires used in this study were forward- and back-translated with subsequent independent verification.

9.6 Data Quality Assurance

Details of the QC and quality assurance measures for this study are provided in the protocol ([Appendix 16.1.1](#)).

9.6.1 Monitoring

The (b) (4) Clinical Research Associate (CRA) ("Monitor") was responsible for the monitoring of the study. Monitoring was performed according to (b) (4) SOPs and as per the monitoring plan agreed with the Sponsor.

The Principal Investigator/head of the investigational site permitted the Monitor to review study data as frequently as considered necessary to ensure that data were being recorded in an adequate manner and that protocol adherence was satisfactory.

The Principal Investigator accessed medical records for the Monitor in order that entries in the CRFs could be verified. The Principal Investigator was expected to ensure that the study adhered to ICH GCP requirements.

9.6.1.1 Pre-investigator and Investigator Meetings

An Investigator meeting was held prior to the site initiation visit. During this meeting, general training for study procedures and specific training on selected procedures were performed and documented (see [Section 9.6.2](#)).

9.6.1.2 Pre-investigation (Site Initiation) Visits

Subsequent to the Investigator's meeting, and before the first subject was screened, a site initiation visit was conducted by the (b) (4) CRA and, if necessary, with the Sponsor or its authorized representatives. The purpose of the site initiation visit was to:

- Meet with the Principal Investigator and applicable staff to review the protocol, study procedures, Principal Investigator obligations according to ICH GCP/other local regulations and monitoring procedures.



- Determine the adequacy of the facilities.
- Inform the Principal Investigator of their responsibilities and the procedures for ensuring adequate and correct documentation.

9.6.1.3 Routine Monitoring Visits

During the study, the Monitor had regular contact with the study site, including interim monitoring visits. The purpose of these visits was to:

- Verify that facilities remained acceptable for the study conduct.
- Verify protocol adherence, the accuracy of data recorded in the source documents and perform IP accountability checks.
- Verify compliance with the applicable regulations.
- Perform source data verification (review of the CRF data against the subject's medical records, and other records relevant to the study), including verification of the informed consent of participating subjects.

Interim monitoring visits were made at regular intervals during the study. The frequency of the monitoring visits was defined in the monitoring plan agreed with the Sponsor.

The Investigator or a designated member of the Investigator's study team was 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.

9.6.1.4 Close-out Visit

The close-out visit was conducted by a CRA from (b) (4) in accordance with (b) (4) SOPs.

The close-out visit occurred on 30 July 2014. All CRFs were completed, monitored, and locked. Database lock occurred on 19 May 2014.

The purpose of the close-out visit was to:

- Ensure all CRF pages were monitored and frozen.
- Perform final IP accountability and ensure the return (or destruction) of remaining IP.
- Final checks to ensure all laboratory samples had been shipped from the site.
- Final check that all ePRO devices had been shipped back.
- Review completion and accuracy of the Investigator File as per Trial Master File checklist including Monitoring Visit Log, Site Responsibility Log, Subject Screening and Enrollment Log, and IP Shipment and Accountability Logs.



- Review procedure for record retention, IRB notification, and publication rights with Principal Investigator.
- Advise site to notify the IRB of study closure, if applicable.

9.6.2 Training of Staff

A formal meeting (Investigator's meeting) was conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative discussed the requirements of the clinical study protocol and related documents and provided training in the relevant systems and other study-specific procedures.

The meeting included the following topics:

- Review of study organization and timelines.
- Review of clinical study protocol and IB.
- Review of CRF and CRF completion guidelines.
- Presentation of Query process.
- Presentation of reporting of protocol deviations.
- Training on use of IP and devices, and IP supplies shipment/documentation.
- Laboratory manuals, kits and labels, laboratory sample shipments.
- Presentation of safety reporting procedures, SAE form, and SAE handling.
- Pregnancy reporting procedures, pregnancy form, and pregnancy handling.
- Refresher training on GCP requirements.
- IXRS randomization procedure and training.
- Electronic data capture system training.
- ePRO system training.
- Review of site monitoring schedule and activities.

Further to the Investigator meeting, the Principal Investigator ensured that appropriate training relevant to the study was provided to all staff involved in the study, and that any new information relevant to the performance of the study was forwarded to the staff involved in a timely manner.

The record of all individuals involved in the study was maintained in the Site Investigator File.



9.6.3 Data Management

Details of the data management activities for this study are provided in Section 11 of the protocol ([Appendix 16.1.1](#)), and all data management activities are described in detail in the Data Management Plan (DMP) and documents specified therein.

9.6.3.1 Data Capture

With the exception of the subject reported outcome data, all results from the clinical assessments were recorded in the source documents by the Principal Investigator and then captured in the CRFs at the study site. The subject questionnaires and the VAS were entered by the subject directly into the ePRO device. Trained study personnel were responsible for capturing the data from the protocol-specified observations, tests, and assessments in the source documents and then transferring the data into the CRF according to the CRF completion guidelines, as necessary.

The Principal Investigator had ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data were accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF was signed by the Principal Investigator to attest that the data contained in the CRF were true and accurate. Any corrections made to source documents were clearly recorded, without obscuring the original values and were accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject was checked against the source documents at the study site by the CRA. Instances of missing or unclear data were discussed with the Principal Investigator for resolution. An CRF was generated for all subjects that signed the informed consent.

A copy of the CRF, subject questionnaires, and VAS used in this study are provided in [Appendix 16.1.2](#). Further details on the collection of study data are provided in Section 11.1.1 of the protocol ([Appendix 16.1.1](#)).

All protocol deviations were entered into an electronic data capture system. The protocol deviation categorization was entered by the Sponsor. Further details on the collection of protocol deviations are provided in Section 11.1.2 of the protocol ([Appendix 16.1.1](#)).

9.6.3.2 Data Handling

All study data was managed by the Data Management Team at Covance. The overall procedures for quality assurance of clinical study data are described in the SOPs of the Data Management Team. The Data Management Team at Covance prepared a DMP to be reviewed and approved by the Sponsor prior to the start of the study. This document described the data management-related procedures and processes in detail.



All data for all subjects enrolled, and screening failures that experienced an AE during the study (from time of informed consent to end of the safety follow-up period) were captured and stored in the study database.

All data collected during the study are property of the Sponsor irrespective of the location of the database and the data management Contract Research Organization (i.e., Covance).

9.6.3.2.1 Data Validation

The data were validated as defined in the DMP and Data Verification Specifications. Discrepancies were reported as defined in the DMP and Data Verification Plan.

Data queries were raised for discrepant or missing data. Changes to data were documented in the database. All entries and changes into the study database are available in an audit trail.

9.6.3.2.2 Coding

Adverse events, medical/surgical history, and prior/concomitant medication were classified according to the terminology of the following Dictionaries:

Medical history: Medical Dictionary for Regulatory Activities (MedDRA[®], Version 16.0).

Adverse events: MedDRA[®], Version 16.0

Medications: World Health Organization - Drug Dictionary Enhanced (WHO-DDE) and Anatomical, Therapeutic Chemical (ATC) classification system, Version Q1 2013.

Device events were classified according to FDA Center for Devices and Radiological Health C54451 Medical Device Problem Codes [16].

9.6.3.2.3 Database Lock

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

After data review by the Sponsor, resolution of all raised queries, and QC of the changed data, the database was declared locked on 19 May 2014.



Any changes to the database after that time could only have been made by written agreement between the Sponsor and the Data Management and Statistical Team at Covance. No changes occurred after database lock.

After study completion, the study database was transferred to the Sponsor in the format specified in the Data Transfer Agreement in Clinical Data Interchange Standards Consortium's Study Data Tabulation Model data structure specifications.

9.6.4 Audits and Inspections

Good Clinical Practice regulations required that independent inspections of clinical program activities were performed. Such inspections could be performed at any time before, during, and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB performed audits or inspections, including source data verification. The purpose of an audit or inspection was to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and that data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. The Principal Investigator or head of the investigational site contacted the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.

The Principal Investigator and study staff were responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that was suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the Principal Investigator confirmed their understanding and agreed to provide access to the necessary documentation and files.

9.7 Planned Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Full details of the statistical analyses were given in the SAP. Any changes to the protocol planned statistical methods are documented in [Section 9.8.2](#). A copy of the SAP is provided in [Appendix 16.1.8](#).

9.7.1.1 General Issues on Evaluation and Presentation of Data

All statistical evaluation and analyses were performed and validated using SAS® Version 9.3.



9.7.1.2 Data Sets for Analysis

Analyses were based on sequence of exposure and actual product exposure. Actual product exposure during single use days was defined as:

- THS 2.2 Menthol: if there was a non-missing time for “Time of First Puff” (from THS 2.2 Menthol consumption page in CRF), and no other product exposure definition was applicable.
- Nicotine replacement therapy gum: if there was a non-missing “Time of First NRT Gum Intake” and “Time of Last Chew” (from the NRT gum consumption page in CRF), and no other product exposure definition was applicable.
- Menthol conventional cigarettes: if there was a non-missing “Time of Lighting the mCC” (from mCC product consumption CRF page), and no other product exposure definition was applicable.

All endpoints (other than safety) were analyzed using the PK analysis sets. Safety was analyzed using the safety population.

9.7.1.2.1 Pharmacokinetic Populations

The analysis populations for the PK endpoints were composed of 2 analysis sets to allow the comparison between THS 2.2 Menthol and mCC (Group-1 PK) separately to the comparison between THS 2.2 Menthol and NRT gum (Group-2 PK).

The PK populations consisted of all randomized subjects who gave informed consent, completed at least 1 of the single-use days (Day 1 or Day 3), and for whom at least 1 PK parameter could be derived. Only subjects with major protocol deviations that impacted the evaluability of the results were excluded from the PK populations.

9.7.1.2.2 Safety Population

The safety population consisted of all subjects who give informed consent and had at least 1 exposure to THS 2.2 Menthol or NRT gum (including the product test at Admission Day regardless of whether or not they were enrolled in the study).

9.7.1.3 Stratification

Each sex and each of the smoking strata (ISO nicotine levels ≤ 0.6 mg and >0.6 mg to ≤ 1 mg) had a quota applied to ensure they represented at least 40% of the total study population.

For analysis, providing there were greater than 4 subjects per category, the following stratifications were used:



- Sex (male or female).
- Menthol CC nicotine level at Admission (ISO nicotine levels ≤ 0.6 mg or >0.6 mg to ≤ 1 mg).

9.7.1.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics were summarized for the Safety and PK populations, and listed for the safety population.

The demographic variables age, sex, race, body weight, height, and BMI were summarized by sequence and overall for the safety population, using the following descriptive statistics: number of subjects, number and percentage of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum, and maximum values. For categorical data, frequency counts and percentages were presented.

Demographics and baseline characteristics were tabulated overall and by the 2 stratification factors (sex and CC ISO nicotine levels at Admission) for the PK populations, as specified in Section 11.1.1 of the SAP in [Appendix 16.1.8](#).

No inferential analyses were presented for demographic and baseline characteristics.

9.7.1.4.1 Cytochrome P450 2A6 Activity at Admission (Day -1)

Plasma CYP2A6 activity was calculated from the metabolic ratio of *trans*-3'-hydroxycotinine and cotinine, both expressed in molar equivalents. The following conversion factors were applied:

Cotinine: The molecular weight is 176.2178 g/mol [22]. For the conversion of cotinine from ng/mL to nmol/L, the result in ng/mL was multiplied by 5.675

Trans-3' hydroxycotinine: The molecular weight is 192.217 g/mol [23]. For the conversion of *trans*-3'-hydroxycotinine from ng/mL to nmol/L, the result in ng/mL was multiplied by 5.202.

The converted results were reported to 3 decimal places and the ratio was reported as a percentage to 2 decimal places. Data were listed and summarized as reported in [Section 9.7.1.4](#).



9.7.1.4.2 Fagerström Test for Nicotine Dependence at Screening

The FTND [18] was conducted at Screening to determine subject's dependence on nicotine. The questionnaire consisted of 6 questions, which subjects answered by themselves.

Table 7 shows the 6 questions and the scores associated with each question.

Table 7 Scoring for the Fagerström Test for Nicotine Dependence

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

The FTND score was derived by summing the individual item scores, only if all items were non-missing (otherwise, the total score was set to missing).

For the FTND total score, descriptive statistics, and frequency tables were categorized into the following categories:

- Mild: 0-3.
- Moderate: 4-6.
- Severe: 7-10.



9.7.1.4.3 Current Menthol Conventional Cigarette Brand Consumption

The current mCC brand(s) smoked by the subject and recorded at Admission (Day -1) was summarized and listed by sequence and study day for the safety population. This included brand name(s), ISO nicotine and tar yields, and number of mCC smoked on a daily basis during the previous 4 weeks. The smoking characteristics and current mCC brand collected at the Screening Visit were listed only.

International Organization for Standardization tar yields at Day -1 were categorized as 1 to 5 mg, 6 to 8 mg, 9 to 10 mg, and >10 mg. International Organization for Standardization nicotine level was categorized as ≤ 0.6 mg, > 0.6 mg to ≤ 1 mg, and > 1 mg. Number of mCC smoked on a daily basis during the previous 4 weeks was categorized as <10, 10 to 19, and >19 cigarettes per day.

9.7.1.4.4 Smoking History and Willingness to Quit Smoking

Smoking history, including whether subjects had smoked for at least the last 3 consecutive years and whether the subject smoked any mCC during the previous 4 weeks was listed by sequence at Screening and Admission (Day -1) where applicable.

The subjects' responses to whether they "plan to quit smoking in next 3 months" were listed at Screening. Readiness to accept interruption of smoking for up to 4 days was listed at Screening and Admission.

9.7.1.4.5 Other Baseline Data

The following data collected at Screening and/or Admission were listed by sequence and subject:

- Cotinine urine test.
- Urine pregnancy test.
- Chest X-ray.
- Urine drug screen.
- Serology.
- Alcohol breath test.
- Prior medication.
- Product test.
- Identification of NRT gum brand.
- Willingness to use THS 2.2 Menthol and NRT gum products.

Prior medication and product test data were also summarized.



9.7.1.5 Pharmacokinetic Assessment Data

Nicotine PK parameters were derived from plasma nicotine versus time data using a non-compartmental technique (Phoenix[®] WinNonlin[®], Version 6.2.1).

The full details of the scheduled collection times of PK blood samples are provided in [Table 6](#).

The actual blood sampling times post-exposure collected in the CRF were used in the computation of the PK parameters, with the exception of the pre-exposure (-15 minutes) blood sampling time which was considered as time zero (T_0).

9.7.1.5.1 Primary Pharmacokinetic Parameters

The following PK parameters for the Group-1 PK population were derived for nicotine on Day 1 and Day 3.

C_{\max} Maximum plasma concentration. C_{\max} was reported as long as there was at least 1 quantifiable concentration post-exposure.

$AUC_{(0-\text{last})}$ Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration (linear trapezoidal method). $AUC_{(0-\text{last})}$ was reported as long as there were at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{\max} .

9.7.1.5.2 Secondary Pharmacokinetic Parameters

The parameters, C_{\max} and $AUC_{(0-\text{last})}$, were derived for the Group-2 PK population as described in [Section 9.7.1.5.1](#).

Additional nicotine PK parameters were derived for the PK population as follows:

$AUC_{(0-t^*)}$ Area under the plasma concentration-time curve from start of product use to the subject-specific time of maximum nicotine concentration following single use of the mCC or NRT gum product, between the THS 2.2 Menthol and mCC, as well as the THS 2.2 Menthol and NRT gum (linear trapezoidal method).



$AUC_{(0-\infty)}$ Area under the plasma concentration-time curve from start of product use extrapolated from t_{last} to infinity, according to:

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

$\%AUC_{extrap}$ Percentage of $AUC_{(0-\infty)}$ that is extrapolated from t_{last} to infinity.

C_{last} Last quantifiable concentration.

t_{last} Time of the last quantifiable concentration.

t_{max} Time to maximum plasma concentration. t_{max} was reported as long as there is at least 1 quantifiable concentration within 1 hour post-exposure.

λ_z Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data.

$t_{1/2}$ Terminal half-life, derived as $\ln(2)/\lambda_z$.

Apparent $t_{1/2}$ was calculated, where possible, over at least 2 half-lives. Where $t_{1/2}$ was estimated over less than 2 half-lives was flagged in the data listings.

Apparent $t_{1/2}$ was not reported if it could only be calculated over a period that was <1.5 half-lives.

The minimum requirement for the calculation of the AUC was the inclusion of at least 3 consecutive plasma concentrations >LLOQ, with at least 1 of these concentrations following C_{max} .

9.7.1.5.3 Descriptive Statistics

For continuous data, summary statistics included the number of subjects, the number and percentage of subjects with missing data, the arithmetic mean, arithmetic SD, median, first and third quartiles, minimum, and maximum; for log-normal data (e.g., the PK parameters: AUC and C_{max}) the geometric mean and geometric coefficient of variation (CV) were presented in addition to the arithmetic mean and SD. For categorical data, frequency counts and percentages were presented.



The geometric CV was calculated according to the following formula:

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

where var = the variance from the log-transformed data.

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

Summary statistics and statistical analyses were performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data were used.

Summaries of each PK populations were produced by product.

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

9.7.1.6 Biomarker Assessment Data

9.7.1.6.1 Exhaled CO and Blood COHb

Full details of the measurements and timings of assessments are provided in [Section 9.5.7.2](#).

Descriptive statistics summarized by exposure were produced separately for all scheduled time points for exhaled CO and COHb assessments at single-use days. This was done on the PK populations, overall, and by the 2 stratification factors (sex, mCC nicotine level at Admission).

Actual values of blood COHb and levels of exhaled CO were listed and summarized. The number of subjects with COHb levels $\leq 2\%$ were summarized for each time point.

In addition line graphs were produced for exposure means (and 95% CI) across all time points.

Values of exhaled CO measured during wash-out, Admission, and Discharge were not analyzed because they were collected only for monitoring purpose. They were, however, listed and summarized and values >10 ppm were flagged as described in [Section 9.5.7.2.1](#).



9.7.1.7 Evaluation of Subjective Effects

9.7.1.7.1 Questionnaire of Smoking Urges-brief

Details of the QSU-brief [21] and timings of the assessment are presented in Section 9.5.7.1. The QSU-brief consists of 10 items as presented in Table 8.

Table 8 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 are 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 were derived [20]. Each factor was a subset that included 5 of the 10 questions as defined in Table 8. Factor 1 represented the desire and intention to smoke with smoking perceived as rewarding, while Factor 2 represented an anticipation of relief from negative effect with an urgent desire to smoke.

The factor and total scores were calculated by averaging non-missing item scores where at least 50% were non-missing; otherwise, the factor or total score was set to missing.

The total score and the 2 factors from the QSU-brief were listed for all scheduled time points and summarized overall and by the 2 stratification factors (sex, mCC nicotine level at Admission) for the PK populations as specified in Section 9.7.1.3. The individual responses to all questions were listed by product, study day, and assessment time points.



9.7.1.7.2 Modified Cigarette Evaluation Questionnaire

Details of the MCEQ [19] and timings of the assessment are presented in [Section 9.5.7.1](#). The MCEQ consists of 12 items as presented in [Table 9](#).

Table 9 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 were derived by averaging the individual non-missing item scores if at least 50% were non-missing; otherwise, the subscale score was set to missing.

The MCEQ domain scores composed of the 3 multi-item subscales and 2 single items from the MCEQ were listed and summarized overall and by the 2 stratification factors (sex, mCC nicotine level at Admission) for the PK populations as specified in [Section 9.7.1.3](#). The individual responses to all questions were listed.

9.7.1.8 Statistical Analysis of Endpoints

For the purpose of the statistical analyses, baseline was defined as the last available time point prior to the product test (THS 2.2 Menthol or NRT gum) at Admission (Day -1) and T₀ was the start time of the product use on Day 1 and Day 3. Start of product use for THS 2.2 Menthol was defined as the time of the first puff. The start time for mCC corresponded to the lighting of the mCC, and the start time of the NRT gum product was the time of the first NRT gum intake.



9.7.1.8.1 Primary Endpoints

Only subjects in the Group-1 PK population who provided evaluable data for both the THS 2.2 Menthol and mCC products were included in the following analyses.

The primary analysis of C_{\max} and $AUC_{(0-\text{last})}$ were 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 [24-27]. The least squares (LS) means for each product were back-transformed by exponentiation and were tabulated together with the ratio (THS 2.2 Menthol : mCC) and 95% CI.

The geometric CV was also presented as:

$$CV(\%) = 100\sqrt{(e^{\text{MSE}} - 1)}$$

where MSE is mean square error of the fitted model residual.

As there were no missing values for the primary PK parameters in Group-1 PK, the sensitivity analyses that were planned if 20% or more PK parameter values were missing were not performed. The planned sensitivity of the primary analyses was a mixed-effects ANOVA model in natural log scale.

To support the interpretation of the PK analysis, the values of nicotine concentration greater than the LLOQ before T_0 were listed together with any PK parameters excluded from the analysis. Listings were 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 was performed as described above, however the data for subjects with their T_0 value >5% of their C_{\max} value were excluded from the analysis.

Planned Sub-groups, Interactions, and Covariates

Exploratory sub-group analyses were described in the final SAP ([Appendix 16.1.8](#)) and were conducted for the primary endpoints in the following sub-groups, provided there were greater than 4 subjects in each category:

- Sex.
- mCC nicotine level at Admission (ISO nicotine level ≤ 0.6 mg or >0.6 mg to ≤ 1 mg).

The primary analysis, described above, was repeated for each level of the 2 sub-groups.



9.7.1.8.2 Secondary Endpoints

Pharmacokinetics

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

Pharmacokinetic parameter and plasma concentration data were also listed along with the details of the actual times after T_0 .

THS 2.2 Menthol versus mCC

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

- The secondary analysis of $AUC_{(0-\infty)}$, $AUC_{(0-t^*)}$, and $t_{1/2}$ was performed on the natural log-transformed parameters using the same ANOVA model as used for the primary analysis (Section 9.7.1.8.1). Only subjects in the Group-1 PK population who provided evaluable data for both the THS 2.2 Menthol and mCC products were included in the analyses.
- The analysis of t_{max} was performed by calculating the difference for each subject (THS 2.2 Menthol - mCC) and obtaining the Hodges-Lehmann [28] 95% CI estimates. The median t_{max} for each product and the median difference between the products along with the 95% CI were presented in the tables.

THS 2.2 Menthol versus NRT Gum

The following analyses were conducted in the Group-2 PK population only:

- The secondary analysis of C_{max} , $AUC_{(0-last)}$, $AUC_{(0-\infty)}$, $AUC_{(0-t^*)}$ and $t_{1/2}$ parameters was performed using the same ANOVA model as used for the primary analysis (Section 9.7.1.8.1).

Only subjects in the Group-2 PK population who provided evaluable data for both the THS 2.2 Menthol and mCC products were included in the analyses.

The analysis of C_{max} and $AUC_{(0-last)}$ tested if the lower bound of the 95% CI for the ratio (THS 2.2 Menthol : NRT gum) was >1.0 at the 0.025 level of significance in order to determine if the rate and the amount of nicotine absorbed via the THS 2.2 Menthol was higher relative to NRT gum. This approach was used to test the following hypothesis for both C_{max} and $AUC_{(0-last)}$ 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 Menthol and NRT gum, respectively. H_0 was 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 Menthol was shorter than in NRT gum, the following hypothesis was evaluated:

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

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

where X_{THS} and X_{NRT} were the median values of the THS 2.2 Menthol and NRT gum, respectively. The time to the maximum concentration was analyzed on the original scale using the Wilcoxon Signed-Rank Test with a type I error $\alpha = 0.025$ (one-sided test), as values were ordinal/discrete, and the assumption of normality could have been questionable.

The analysis of t_{max} was performed by calculating the difference for each subject (THS 2.2 Menthol - NRT gum) and obtaining the Hodges-Lehmann 95% CI estimates [28]. The median t_{max} for each product and the median difference between the products along with the 95% CI were presented.

As there were 10% or less missing data for all of the secondary PK parameters in both the Group-1 and Group-2 PK populations, the sensitivity analyses that were planned if 20% or more PK parameter values were missing were not performed. The planned sensitivity of the secondary analyses was a mixed-effects ANOVA model in natural log scale.

No time information was imputed for the computation of the primary PK parameters, therefore, no supportive analysis was conducted.

Exhaled CO and Blood COHb

The analysis of the exhaled CO during single use and log transformed blood COHb levels were performed using a mixed-effects ANOVA with a restricted maximum likelihood (REML) method to estimate mean differences and variances separately for THS 2.2 Menthol versus mCC and THS 2.2 Menthol versus NRT gum, using heterogeneous compound symmetry covariance structure in order to allow unequal variances at the different time points [29]. Subjects nested within sequence were used as random effects and sequence, period, product, and product*time point were used as fixed effect factors. The model was evaluated including all of the different assessment time points (excluding the assessment prior to T_0). In addition, time point was treated as a repeated measurement.



For the analysis of CO breath test, the main comparison was the difference over all time points. The LS means for each product, overall differences (THS 2.2 Menthol - mCC or THS 2.2 Menthol - NRT gum as appropriate), and the differences at each time point were 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 were produced.

For the COHb analysis, the main comparison was the ratio over all time points. For each product, LS means were back-transformed by exponentiation and presented in tables together with the point and interval (95% CI) estimate of the overall ratio (THS 2.2 Menthol: mCC or THS 2.2 Menthol: 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 were produced.

Questionnaire of Smoking Urges-brief

Line graphs were produced for the total score and factor means (and 95% CI) across all time points.

The analysis of the subjective effects of smoking (the total score, and Factor 1 and Factor 2 from the QSU-brief) was performed using the same mixed-effects ANOVA adopted for the analysis of the CO breath test described in [Section 9.7.1.8.2](#). The time points of the THS 2.2 Menthol assessment schedule were considered in the analysis, and data at T₀ +15min for NRT gum were imputed as described in [Section 11.3.3](#).

To evaluate the sensitivity to the distributional assumptions for the QSU-brief (for more detail see Section 11.6.3 of the SAP in [Appendix 16.1.8](#)) questionnaire scores, point, and 95% CI estimates were also assessed by means of the percentile bootstrap technique, using 2000 bootstrap samples which preserved the number of subjects per sequence.

Where the model failed to converge for any bootstrap sample, estimates of $+\infty$ and $-\infty$ were added to the results dataset before the CIs were calculated.

The main comparison was the mean difference over all time points; LS means for each product, the overall mean difference (THS 2.2 Menthol - mCC or THS 2.2 Menthol - NRT gum as appropriate) and the mean differences at each time point were 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 were produced.

Modified Cigarette Evaluation Questionnaire

A mixed-effects ANOVA model was used to estimate mean THS 2.2 Menthol - mCC differences of the MCEQ domain scores and variances, with a REML method, using heterogeneous compound symmetry covariance structure [\[29\]](#). Subjects within sequence



were used as random effects and fixed effects were period, sequence, and product exposure.

The model did not converge using the heterogeneous compound symmetry covariance structure. This was replaced with a heterogeneous autoregressive covariance structure and again the model did not converge and was replaced with variance component, which allowed the model to converge.

Least square means for each product and the point and 95% CI estimate of the overall difference (THS 2.2 Menthol - mCC) were presented in the tables.

To evaluate the sensitivity to the distributional assumptions for the MCEQ (for more detail see Section 11.6.3 of the SAP in [Appendix 16.1.8](#)) questionnaire scores, point, and 95% CI estimates were also assessed by means of the percentile bootstrap technique, using 2000 bootstrap samples which preserved the number of subjects per sequence.

9.7.2 Post-hoc Analyses

Any post-hoc and additional exploratory analyses completed to support planned study analyses, which were not identified in the protocol or SAP, were documented and reported as applicable. Any results from these unplanned analyses are described in [Section 9.8.2](#).

9.7.3 Safety Data Summary

The safety variables monitored in this study are described in [Section 9.5.3](#).

All AEs occurring from the signing of informed consent were recorded electronically. The AE listings included 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 that occurred after the product test of THS 2.2 Menthol or NRT gum were included in the summary tables.

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

Partial dates were not imputed, but assumptions were made as follows to assign to exposure-emergent or not:



Date information	Assign as
Partial date, e.g., May 2012 or 2011. If month/year was the same as, or later than the month and/or year of Screening.	Exposure-emergent
Partial date, e.g., May 2012 or 2011. If month and/or year was earlier than the month and/or year of Screening.	Not exposure-emergent

9.7.3.1 Adverse Events

A general summary table of AEs was presented by sequence and overall, including:

- The number of events and the number and percentage of subjects reporting at least 1 AE.
- The number of events and the number and percentage of subjects reporting at least 1 study product-related AE, broken down by product relatedness (related to THS 2.2 Menthol / mCC, related to NRT gum) and expectedness (expected, not expected).
- The number of AEs and the number and percentage of subjects reporting at least 1 AE broken down by severity. Where AE severity changed, only the most severe was included.
- The number of events and the number and percentage of subjects reporting at least 1 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, or other action taken.
- The number of AEs and the number and percentage of subjects reporting at least 1 AE related to study procedure.

Additional summary tables of AEs were 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 system organ class (SOC) and preferred term (PT) coded according to MedDRA® (Version 16.0)

- The number of AEs and the number and percentage of subjects reporting at least 1 AE.
- The number of AEs and the number and percentage of subjects with at least one AE related to product exposure and expectedness for IP (THS 2.2 Menthol or mCC) and reference point product (NRT gum).
- The number of AEs and the number and percentage of subjects with at least 1 AE leading to study discontinuation.
- The number of AEs and the number and percentage of subjects with at least 1 AE related to study procedure.



- The number of AEs and the number and percentage of subjects with at least 1 AE by severity (mild, moderate, severe).

If a subject had more than 1 occurrence of the same AE, the subject was 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 an AE was to be counted as severe.

9.7.3.2 Prior and Concomitant Medication

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

All medications were listed by sequence using PT and ATC codes (WHO-DDE, Q1 2013). A flag was presented on the listing indicating whether the medication was prior or concomitant. Partial dates were not imputed, but assumptions were made as described in Section 11.6.4.5.1 of the SAP (see [Appendix 16.1.8](#)).

Prior and concomitant medications were listed by sequence. Concomitant medications were summarized for the safety population showing the number (%) of subjects who used the medication at least once by sequence, by ATC first and second level medical terms, and by preferred drug name. Listings were provided by sequence and displayed original dates (no imputation).

9.7.3.3 Laboratory Safety Parameters

[Table 5](#) lists the hematology, clinical chemistry, and urine analysis parameters assessed in this study.

The grading scheme used in the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] Version 4.03) was used by the Principal Investigator to assess abnormal laboratory AEs. These CTCAE grades were derived programmatically in the creation of the datasets.

All laboratory data were 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 Principal Investigator comment) were tabulated for laboratory parameters.

Listings for the clinical laboratory data included the following information: normal/high/low (with respect to reference range), abnormal clinically relevant (as



defined by comments), the Principal Investigator comments, the change from baseline Investigator and the CTCAE grade. Only CTCAE grades greater than zero were presented.

9.7.3.4 Physical Examination

Physical examination data recorded at the Screening visit, Admission (Day -1), and Discharge (Day 4 or at the day of withdrawal for withdrawn subjects) were listed by sequence. Subject data with abnormal and clinically significant abnormal physical examination findings were flagged. The number of subjects (%) with normal, abnormal, and clinically significant abnormal results was 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) were listed together with BMI. Descriptive statistics of body weight, body height, and BMI, at Admission and Discharge, were presented by sequence and overall.

The reported BMI was calculated using the body weight and height as described in [Section 9.5.3.2](#). The BMI was categorized into: underweight ($<18.5 \text{ kg/m}^2$), normal range (≥ 18.5 to $<25.0 \text{ kg/m}^2$), overweight (≥ 25.0 to $<30.0 \text{ kg/m}^2$), and obese ($\geq 30.0 \text{ kg/m}^2$).

9.7.3.5 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate measured during the study were listed by sequence and study day. Descriptive statistics were 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 were summarized together with changes from baseline.

9.7.3.6 Electrocardiogram

Details of the ECG assessments and timings are provided in [Section 9.5.3.5](#). Electrocardiogram data, values and normality evaluations were listed by sequence and study day (Screening, Day 1, and Day 3) together with changes and shifts in normality from baseline (Screening). Electrocardiogram data from subjects which had significant clinical findings were highlighted in listings.

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



9.7.3.7 Spirometry

The assessed spirometry parameters included:

- FEV₁.
- FVC.
- FEV₁/FVC.
- Predicted FEV₁.
- Percent of predicted FEV₁ (% pred).
- Predicted FVC.
- Percent of predicted FVC (% pred).
- Measurement interpretation (categories: normal, abnormal, abnormal clinically significant).

The above data were collected at Screening, Admission and Discharge. At Screening, data were collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator.

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

Descriptive statistics were presented for FEV₁ (L), FEV₁ (% pred), FVC (L), FVC (%pred), and FEV₁/FVC at baseline, and discharge by sequence, and overall. Spirometry data were summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results.

9.7.3.8 Medical and Surgical History

Medical history and concomitant diseases recorded at the Screening Visit were coded using MedDRA[®] (Version 16.0) and listed separately by sequence, SOC, and PT within SOC.

9.7.3.9 Assessment of Cough

Cough questionnaire was completed from Day 0 to Day 4 (prior to product use on Day 1 and Day 3). Details on cough assessment are provided in [Section 9.5.7.1](#). The number and percentage of subjects reporting a cough were summarized by sequence and overall. The responses to individual questionnaire items, including the VAS evaluating the level of cough experienced and 3 Likert scales measuring the intensity, the frequency of cough, and the amount of sputum production were 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 observations were listed.

9.7.3.10 Device Malfunction or Misuse

All events relating to the THS 2.2 Menthol device were 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.

A summary table of device events was presented by sequence and overall, including:

- Number of device events and the number and percentage of subjects reporting at least 1 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 (Holder stops heating, Holder does not charge, Holder LED blinking red, smoking experience does not start, electronic malfunction, other).

Device events and inventory were listed by sequence. Data collected during Screening were listed but not summarized.

9.7.3.11 Product Compliance

Levels of CO in exhaled breath were measured to evaluate the exposure to CO (see [Section 9.5.7.2](#)) and to monitor compliance during the following study days:

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

Carbon monoxide data were listed and summarized by sequence for all study days and time points as a continuous variable and with the categorization ≤ 10 ppm and >10 ppm.

Values above 10 ppm were highlighted in listings and considered as non-compliant if such values were observed prior to first product use on the single-use days for all exposures or throughout the single use days for NRT gum exposure. During the wash-out days values above 10 ppm were considered non-compliant on Day 2, but were expected on Day 0 because smoking was permitted *ad libitum* during Day -1. Carbon monoxide data leading to exclusion of subjects from the analysis were evaluated during the pre-analysis blind data review.



The number and percentage of subjects considered as non-compliant during the study were tabulated by sequence and study day for the randomized population.

9.7.4 Interim Analyses

No interim analysis was planned or conducted for this study.

9.7.5 Determination of Sample Size

A total of 62 subjects were randomized. This sample size was the sum of the sample size requirements for the THS 2.2 Menthol : mCC comparison and the THS 2.2 Menthol : NRT gum comparison.

The estimates for the within-subject CV for nicotine C_{\max} (36%) and $AUC_{(0-\text{last})}$ (21%) were based on the data collected in the ZRHX-PK-02 clinical study [30] comparing the nicotine PK profiles of THS 2.1, the predecessor of THS 2.2 Menthol (with 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 Menthol : NRT gum comparison.

Anticipated mean C_{\max} and $AUC_{(0-\text{last})}$ for THS 2.2 Menthol and mCC were based on data from the ZRHX-PK-02 study [30]. Anticipated mean C_{\max} and $AUC_{(0-\text{last})}$ for NRT gum were based on data reported by Dautzenberg et al. [31].

The sample sizes of this study assumed a dropout 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 [24]. The SAS implementation of the method published by Beal et al. [32] was adopted to estimate the probability of obtaining at most the target 95% CI of $\pm 20\%$.

THS 2.2 Menthol : mCC Comparison

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



THS 2.2 Menthol : NRT Gum Comparison

A total of 18 subjects were needed to estimate the geometrical mean $AUC_{(0-last)}$ ratio between THS 2.2 Menthol 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 Menthol and NRT gum. This sample size was 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 Menthol and NRT gum, exceeding 1.00, assuming a geometrical mean ratio between THS 2.2 Menthol and NRT gum of 2.00.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The study was conducted according to the final protocol dated 21 June 2013. There were no protocol amendments for this study.

9.8.2 Changes in the Planned Analyses

The following changes to the analyses planned in the protocol were made before the database lock:

- Safety analyses were not performed by product. Due to the study design it was determined that this presentation was not clear because of the product test at Admission, and it was considered that the selection of arbitrary time points for defining periods associated to the different study products could be misleading. In addition, safety laboratory evaluations were only collected prior to any product use and following the use of both products.
- Shift tables for safety endpoints were not produced for this study because the relevant information was provided in listings.
- Statistical analysis for blood COHb (%) and exhaled CO (ppm) measurements and the QSU-brief questionnaire data were 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 THS 2.2 Menthol effects over time. The main comparison between products was the comparison over all time points.
- Spirometry predicted values were not standardized to the NHANES III predicted set as planned in the protocol. Predicted FEV₁ and FVC were calculated according to the formula recommended by the Japanese Respiratory Society [33] for Japanese population.
- Results of the HIV 1/2 serology tests were not transferred to Covance due to Japanese privacy laws, therefore these results could not be presented in listings.



The following changes to the analyses planned in the protocol were made after the database lock:

- Willingness to quit smoking was not added to [Appendix 15, Listing 15.3.1.4](#) as relevant data was already available from the inclusion/exclusion criteria data.
- As there was no PK blood sampling between 12 and 24 hours post-product use, and a number of subjects had quantifiable nicotine concentrations at 24 hours post-product use, additional $t_{1/2}$ estimates and area under plasma concentration-time curve values were calculated over the 0 to 12 hours post-use time period ($t_{1/2(0-12)}$ and $AUC_{(0-12)}$). These results are presented in a separate report.



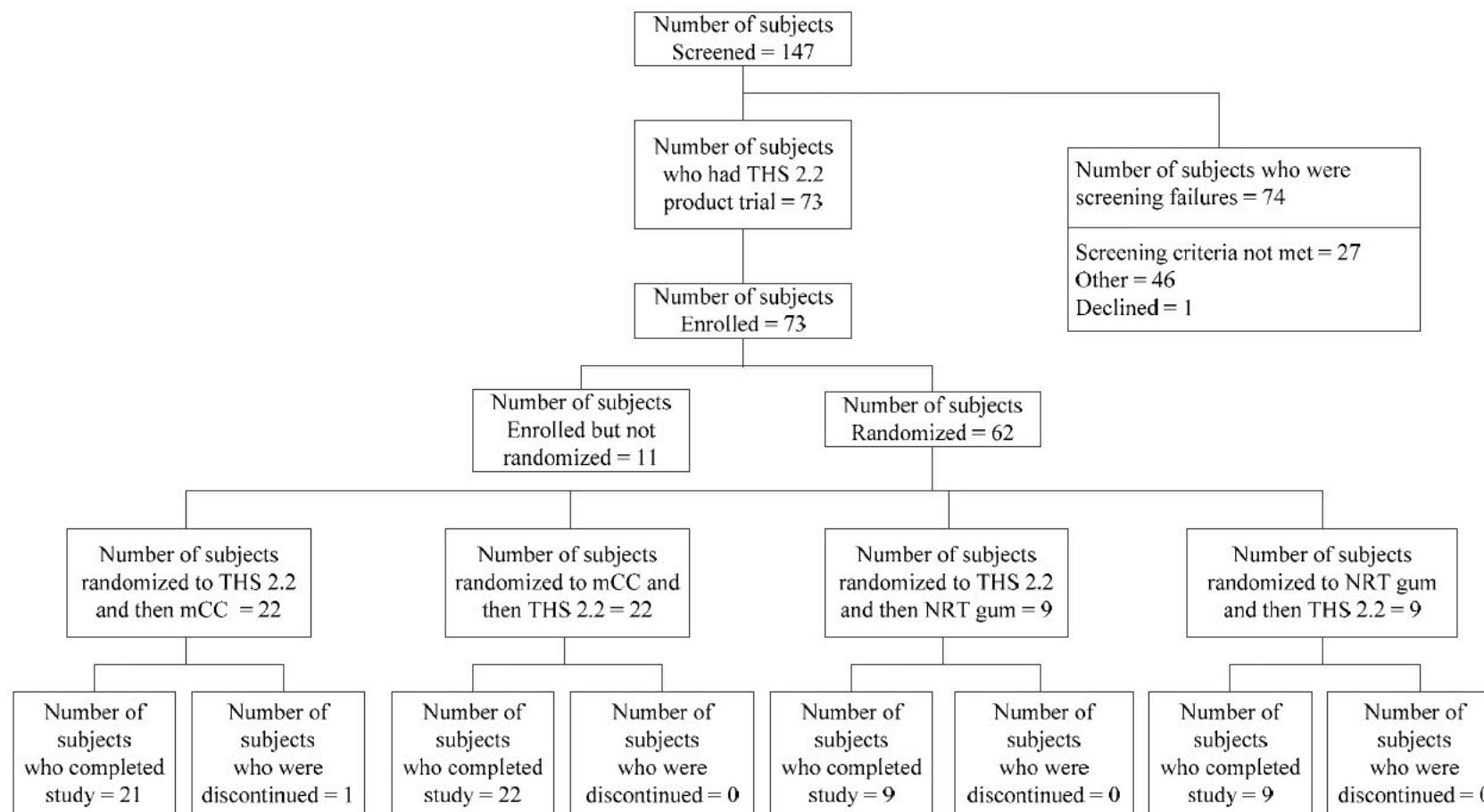
10 STUDY SUBJECTS

10.1 Disposition of Subjects

Subject disposition data are listed by subject in [Appendix 15, Listing 15.3.1.7](#).

Subject disposition data are summarized in [Appendix 15, Table 15.2.1.1](#) (disposition of subjects), [Table 15.2.1.2](#) (reasons for discontinuation), and shown in [Figure 2](#).

Subject eligibility data are listed by subject in [Appendix 15, Listing 15.3.1.1](#) (inclusion and exclusion criteria and responses).

**Figure 2 Disposition of Subjects**

Abbreviations: mCC = menthol conventional cigarette; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Table 15.2.1.1.](#)



Reasons for subject discontinuation are summarized for all subjects in [Table 10](#).

Table 10 Subject Discontinuations for All Randomized Subjects

	Sequence				Overall Randomized (N=62)
	THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NRT gum (N=9)	NRT gum - THS 2.2 Menthol (N=9)	
Total number of discontinuations – n (%)	1 (4.5%)	0	0	0	1 (1.6%)
Reason for discontinuation					
Adverse events – n (%)	0	0	0	0	0
Protocol violation – n (%)	0	0	0	0	0
Withdrawal by subject – n (%)	1 (4.5%)	0	0	0	1 (1.6%)
Lost to follow-up – n (%)	0	0	0	0	0
Other – n (%)	0	0	0	0	0

Abbreviations: mCC = menthol conventional cigarette; N = number of subjects randomized; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Percentages were calculated using the N of subjects in the column headers.

Data Source: [Appendix 15, Table 15.2.1.2](#).

Of the 147 subjects who were screened, 73 subjects tried the THS 2.2 Menthol product during the product trial, and 74 subjects were screening failures. Of the 73 subjects that tried the THS 2.2 product, 11 subjects were enrolled but not randomized as they were back up subjects, and 62 subjects were randomized.

Of the 62 subjects randomized, 22 subjects were randomized to receive THS 2.2 Menthol followed by mCC, 22 subjects were randomized to receive mCC followed by THS 2.2 Menthol, 9 subjects were randomized to receive THS 2.2 Menthol followed by NRT gum, and 9 subjects were randomized to receive NRT gum followed by THS 2.2 Menthol.

A total of 61 subjects completed the study. One subject (Subject 0107, THS 2.2 Menthol – mCC sequence) voluntarily withdrew after product use on Day 1 ([Appendix 15, Table 15.2.1.2](#)).

10.2 Protocol Deviations

Protocol deviations are listed in [Appendix 15, Listing 15.3.1.11](#).

The number and percent of subjects with major and minor protocol deviations are summarized in [Appendix 15, Table 15.2.1.3](#) and shown in [Table 11](#).

**Table 11 Protocol Deviations**

	Sequence					Overall Safety (N=73)
	THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NRT gum (N=9)	NRT gum - THS 2.2 Menthol (N=9)	Exposed not randomized (N=11)	
Number (%) of subjects with:						
Major protocol deviations	0	0	0	0	1 (9.1%)	1 (1.4%)
Minor protocol deviations						
Time schedule deviation	21 (95.5%)	22 (100%)	9 (100%)	9 (100%)	0	61 (83.6%)
Procedure violation	5 (22.7%)	3 (13.6%)	2 (22.2%)	2 (22.2%)	11 (100%)	23 (31.5%)

Abbreviations: mCC = menthol conventional cigarette; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Percentages were calculated using the N of subjects in the column headers.

Data Source: [Appendix 15, Table 15.2.1.3](#).

None of the randomized subjects reported any major protocol deviations. A major deviation was reported for 1 subject who was exposed but not randomized; Subject 0087 was screened twice and was enrolled at the second screening with a second subject number in error. Consequently, the subject number 0117 was removed.

All enrolled subjects had minor protocol deviations relating to timing windows of assessments or minor procedure violations. None of the minor protocol violations resulted in any subject being excluded from the analysis.

10.3 Data Sets Analyzed

The number of subjects in each analysis population are summarized in [Table 12](#).

**Table 12 Summary of Analysis Populations by Stratification Factors and Product**

	Population			
	Safety (N=73)	Overall PK (N=61)	Group-1 PK (N=43)	Group-2 PK (N=18)
Sex				
Male, n (%)	37 (50.7%)	32 (52.5%)	23 (53.5%)	9 (50.0%)
Female, n (%)	36 (49.3%)	29 (47.5%)	20 (46.5%)	9 (50.0%)
ISO nicotine level				
≤0.6 mg, n (%)	44 (60.3%)	35 (57.4%)	25 (58.1%)	10 (55.6%)
>0.6 to ≤1 mg, n (%)	29 (39.7%)	26 (42.6%)	18 (41.9%)	8 (44.4%)

Abbreviations: ISO = International Organization for Standardization; N = number of subjects.

Data Source: [Appendix 15](#), [Table 15.2.1.4.1](#), [Table 15.2.1.4.2](#), and [Table 15.2.1.4.3](#).

The overall PK population consisted of 61 subjects. A single randomized subject (Subject 0107, THS 2.2 – mCC sequence) withdrew from the study on Day 1, so this subject was excluded from the PK analysis as she did not complete at least 1 single exposure day. Data from subjects excluded from the analysis of primary and secondary endpoints are reported in [Appendix 15](#), [Listing 15.3.2.7](#).

The primary endpoints were analyzed using the Group-1 PK population. The Group-1 PK population consisted of 43 subjects: 21 subjects in the THS 2.2 Menthol – mCC sequence and 22 subjects in the mCC – THS 2.2 Menthol sequence.

The secondary endpoints were analyzed using the Group-1 and Group-2 PK populations. The Group-2 PK population consisted of 18 subjects: 9 subjects in the THS 2.2 Menthol – NRT gum sequence and 9 subjects in the NRT gum – THS 2.2 Menthol sequence.

The safety endpoints were analyzed using the safety population. The safety population consisted of 73 enrolled subjects: 62 randomized subjects and 11 non-randomized subjects. The non-randomized subjects included into the safety population consisted of the 11 enrolled but not randomized subjects who had the THS 2.2 Menthol product trial on Day -1.

In each study population, the distribution between male and female subjects was comparable. The distribution of subjects within each ISO nicotine level was not even, with a lower number of high nicotine level smokers in all study populations, however the number represented at least 40% of the Overall, Group-1, and Group-2 PK populations. The distribution of high nicotine level smokers within the female sub-population was lower than the number of low nicotine level smokers (see [Appendix 15](#), [Table 15.2.1.4.2.1](#), [Table 15.2.1.4.2.2](#), [Table 15.2.1.4.3.1](#), and [Table 15.2.1.4.3.2](#)).



10.4 Demographics and Other Baseline Characteristics

10.4.1 Demographics

Subject demographic data are listed in [Appendix 15, Listing 15.3.1.6](#), and are summarized along with baseline characteristics data for the safety, overall PK, Group-1 PK, and Group-2 PK populations in [Appendix 15, Table 15.2.1.4.1, Table 15.2.1.4.2, and Table 15.2.1.4.3](#).

An overview of demographics and baseline characteristics is shown for the safety, overall PK, Group-1 PK, and Group-2 PK populations in [Table 13](#).

Table 13 Summary of Demographic Data

Variable	Statistic	Population			
		Safety (N=73)	Overall PK (N=61)	Group-1 PK (N=43)	Group-2 PK (N=18)
Ethnicity					
Japanese	n (%)	73 (100%)	61 (100%)	43 (100%)	18 (100%)
Age (years)	Mean (SD)	33.1 (9.63)	32.6 (9.44)	33.4 (10.03)	30.7 (7.80)
	Median	30.0	29.0	31.0	28.0
	Min, Max	23, 61	23, 61	23, 61	23, 44
Height (m)	Mean (SD)	1.655 (0.0812)	1.661 (0.0801)	1.666 (0.0742)	1.651 (0.0941)
	Median	1.650	1.670	1.670	1.660
	Min, Max	1.50, 1.86	1.50, 1.86	1.53, 1.80	1.50, 1.86
Weight (kg)	Mean (SD)	61.44 (8.814)	62.21 (8.835)	62.05 (7.989)	62.59 (10.843)
	Median	60.80	61.80	61.80	60.95
	Min, Max	46.0, 82.2	46.0, 82.2	46.0, 78.7	48.2, 82.2
BMI (kg/m ²)	Mean (SD)	22.38 (2.349)	22.49 (2.374)	22.34 (2.324)	22.86 (2.520)
	Median	22.21	22.28	22.10	23.13
	Min, Max	18.7, 30.4	18.7, 30.4	18.7, 30.4	18.8, 28.4
Daily mCC consumption at Admission					
10 to 19 cig/day	n (%)	44 (60.3%)	36 (59.0%)	25 (58.1%)	11 (61.1%)
>19 cig/day	n (%)	29 (39.7%)	25 (41.0%)	18 (41.9%)	7 (38.9%)

Abbreviations: BMI = body mass index; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; PK = pharmacokinetic; SD = standard deviation.

Data Source: [Appendix 15, Table 15.2.1.4.1, Table 15.2.1.4.2, and Table 15.2.1.4.3](#).



All subjects were Japanese with a similar distribution between age, height, weight, and BMI between the study populations.

Baseline BMI data are further summarized in [Appendix 15, Table 15.2.1.4.2](#) and [Table 15.2.1.4.3](#) by the following categories: underweight ($<18.5 \text{ kg/m}^2$), normal weight (≥ 18.5 to $<25.0 \text{ kg/m}^2$), overweight (≥ 25.0 to $<30.0 \text{ kg/m}^2$), and obese ($\geq 30.0 \text{ kg/m}^2$).

10.4.2 Medical and Surgical History

Medical history is presented by subject in [Appendix 15, Listing 15.3.1.8.1](#) and summarized by SOC and PT for the safety population in [Appendix 15, Table 15.2.1.6](#).

No subjects reported any medical history findings at Screening.

10.4.3 CYP2A6 Activity at Admission

Cytochrome P450 2A6 activity in plasma at Admission (Day -1) is listed by sequence in [Appendix 15, Listing 15.3.1.10](#) and summarized for the safety, Group-1 PK, and Group-2 PK populations in [Appendix 15, Table 15.2.1.4.1](#), [Table 15.2.1.4.2](#), and [Table 15.2.1.4.3](#), respectively.

No notable differences were observed between the 4 sequences, or between the Group-1 and Group-2 PK populations, with regard to baseline CYP2A6 activity.

Overall, the 61 randomized subjects in the PK population had a mean baseline CYP2A6 activity of 26.944% (SD = 20.5127%). Furthermore, no notable differences were observed between males and females or between subjects who smoked mCC with a nicotine yield of $\leq 0.6 \text{ mg}$ and subjects who smoked mCC with a nicotine yield of >0.6 to $\leq 1 \text{ mg}$.

10.4.4 Fagerström Test for Nicotine Dependence at Screening

Individual subject responses to the FTND are presented by sequence in [Appendix 15, Listing 15.3.1.9](#).

The FTND overall classification is summarized by category (mild: 0 to 3; moderate: 4 to 6; severe: 7 to 10) for the safety, Group-1 PK, and Group-2 PK populations in [Appendix 15, Table 15.2.1.4.1](#), [Table 15.2.1.4.2](#), and [Table 15.2.1.4.3](#), respectively.

The distribution of subjects in classification category, and the mean total scores were comparable across sequences and study populations. Overall the majority of enrolled subjects (49.3%) had an FTND overall classification of moderate. Six subjects (8.2%) had an FTND overall classification of severe: 2 subjects in the Group-1 PK population, 2 subjects in the Group-2 PK population, and 1 enrolled not randomized subject. The remaining subject was assigned to the THS 2.2 Menthol – mCC sequence but withdrew



voluntarily and was therefore not included in the PK population. Of the 6 subjects, 3 were male and 3 subjects were female, 4 and 2 subjects smoked mCC with nicotine yields of ≤ 0.6 mg and >0.6 to ≤ 1 mg, respectively, 4 subjects smoked 10 to 19 cigarettes/day and 2 subjects smoked >19 cigarettes/day.

10.4.5 Current Cigarette Brand Consumption

The current mCC brand(s) smoked by the subject (including brand name, ISO tar and nicotine yields), as recorded at the Screening Visit and at Admission (Day -1), are listed by sequence in [Appendix 15, Listing 15.3.1.2](#).

The ISO tar yields (mg) recorded at Admission (Day -1) are summarized using descriptive statistics, and by the following categories: 1 to 5 mg, 6 to 8 mg, 9 to 10 mg, and >10 mg, for the safety, Group-1 PK, and Group-2 PK populations in [Appendix 15, Table 15.2.1.4.1](#), [Table 15.2.1.4.2](#), and [Table 15.2.1.4.3](#), respectively.

The current mCC brand names recorded at Admission (Day -1) are summarized in [Appendix 15, Table 15.2.1.5](#).

Among the enrolled subjects, 9 subjects smoked cigarettes with an ISO tar yield of >10 mg; 5 subjects in the THS 2.2 Menthol – mCC sequence, 2 subjects in the mCC – THS 2.2 Menthol sequence, and 2 enrolled not randomized subjects. Seven of these subjects were male and 2 subjects (both in the THS 2.2 Menthol – mCC sequence) were female. No subjects in the Group-2 PK population smoked cigarettes with an ISO tar yield >10 mg. Therefore, there were a greater number of subjects who smoked cigarettes with an ISO tar yield of >10 mg in the THS 2.2 Menthol – mCC sequence (22.7%) compared to the other 3 sequences (0% to 9.1%). The incidence of subjects who smoked cigarettes with an ISO tar yield of 6 to 8 mg was comparable between the mCC – THS 2.2 Menthol, THS 2.2 Menthol – NRT gum, and NRT gum – THS 2.2 Menthol sequences (33.3% to 50.0%) but was lower in the THS 2.2 Menthol – mCC sequence (18.2%). The incidence of subjects who smoked cigarettes with an ISO tar yield of 1 to 5 mg and 9 to 10 mg was comparable between sequences.

In the Group-1 PK population, a greater number of female subjects smoked cigarettes with an ISO tar yield of 1 to 5 mg (65.0%) than male subjects (26.1%). Conversely, the number of male subjects who smoked cigarettes with an ISO tar yield of 6 to 8 mg (47.8%) was higher than the number of female subjects (20.0%), and the number of male subjects who smoked cigarettes with an ISO tar yield of >10 mg (21.7%) was also higher than the number of female subjects (10.0%). No such disparity was seen for the Group-2 PK population.



10.4.6 Smoking History and Willingness to Quit Smoking

Smoking history responses (including “plan to quit smoking in next 3 months” responses) at the Screening Visit and at Admission (Day -1), are listed by sequence in [Appendix 15, Listing 15.3.1.3](#).

All enrolled subjects had a smoking history of at least 3 years of consecutive smoking. It was also established that no subject planned to quit within the next 3 months when asked at the Screening Visit.

The number of cigarettes smoked per day on average during the previous 4 weeks prior to Screening was categorized into 10 to 19 or >19 cigarettes/day. The number (and disposition) of subjects who smoked 10 to 19 and >19 cigarettes/day at baseline are summarized in [Table 13](#) in [Section 10.4.1](#). Amongst the 73 enrolled subjects, 44 (60.3%) smoked 10 to 19 cigarettes/day and 29 subjects (39.7%) smoked >19 cigarettes/day.

10.4.7 Other Baseline Data

The following baseline data are listed by sequence for all subjects ([Appendix 15, Listing 15.3.1.5](#)):

- Chest X-ray findings at the Screening Visit were normal for all subjects.
- Urine cotinine screen at the Screening Visit and at Admission were positive for all subjects.
- Urine drug screen and alcohol breath test at the Screening Visit and at Admission were negative for all subjects.
- Serology tests at the Screening Visit. Tests for hepatitis B surface antigen, HIV 1/2, and hepatitis C virus antibody were negative for all subjects. Results of the HIV 1/2 serology tests could not be transferred to Covance due to Japanese privacy laws, therefore these results are not presented in listings.
- Urine pregnancy test results at the Screening Visit, Admission, and at the Day of Discharge were negative for all 30 randomized female subjects and 6 enrolled but not randomized female subjects.

10.4.8 Concomitant Diseases

Concomitant diseases are presented by subject in [Appendix 15, Listing 15.3.1.8.2](#).

No subjects reported any concomitant diseases during the study.



10.4.9 Prior and Concomitant Medications

Prior and concomitant medications are listed for all subjects in [Appendix 15, Listings 15.3.6.3.1 and 15.3.6.3.2](#).

No subjects reported the use of prior medication and no subjects received concomitant medication during the study.

10.5 Extent of Exposure to Investigational Product

Details of the subjects' daily consumption of mCC, including *ad libitum* use on Day -1 are presented in [Appendix 15, Listing 15.3.2.1.1](#). Details of subject's THS Menthol Tobacco Stick consumption on single-use days and the product trial at Admission are presented in [Appendix 15, Listing 15.3.2.1.2](#). Details of subject's NRT gum use on single-use days and the product trial at Admission are presented in [Appendix 15, Listing 15.3.2.1.3](#).

Descriptive statistics of product use for the safety population are summarized in [Appendix 15, Table 15.2.2.1](#).

All randomized subjects completed the product test at Admission. All subjects used only 1 THS Menthol Tobacco Stick.

All subjects received the IP and NRT gum according to the randomization schedule, with the exception of Subject 0107 (THS 2.2 Menthol – mCC) who did not receive her assigned product on Day 3 due to voluntarily withdrawing from the study on Day 1.

10.6 Compliance to Investigational Product

Compliance with the IP was ensured by controlling the access of smokers to the mCC and THS Menthol Tobacco Sticks during the entire confinement period. In addition, in subjects using NRT gum, levels of CO in exhaled breath were measured to monitor compliance during wash-out to ensure that the subjects had not smoked any cigarettes.

The exhaled CO levels (ppm) for all study days are presented by sequence for all subjects in [Appendix 15, Listing 15.3.3.5](#), with levels >10 ppm considered as non-compliant for subjects on Day 2 in subjects using NRT gum. Descriptive statistics of compliance for all study days are presented in [Appendix 15, Table 15.2.5.1](#).

All randomized subjects were compliant to product use during the study.



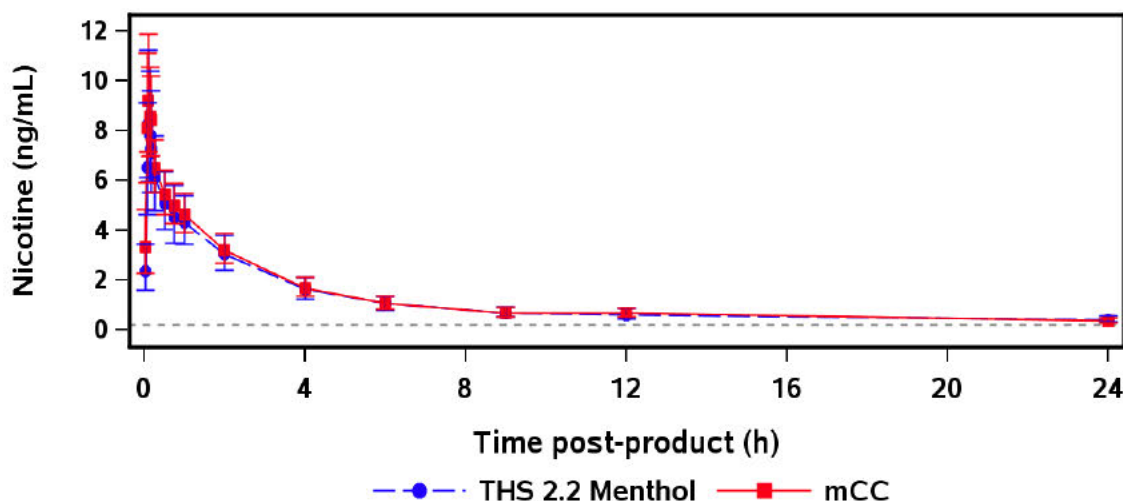
11 ENDPOINT EVALUATIONS AND ADDITIONAL ANALYSES

Plasma nicotine concentrations (ng/mL) following single use of THS 2.2 Menthol and mCC, and the nominal and actual times of PK blood sample collection are listed by subject in [Appendix 15, Listing 15.3.3.2](#). Plasma nicotine concentrations are summarized for the Group-1 PK population by each scheduled time point in [Appendix 15, Table 15.2.4.6](#).

Plasma nicotine concentration profiles for all subjects following single use of THS 2.2 Menthol and mCC are shown for the Group-1 PK population in [Appendix 15, Figure 15.1.2.2.1](#) (linear and semi-logarithmic scales). Plasma nicotine concentration profiles by individual subject following single use of THS 2.2 Menthol and mCC are shown for the PK population in [Appendix 15, Figure 15.1.2.3](#) (linear and semi-logarithmic scales).

Geometric mean plasma nicotine concentration-time profiles following single use are shown by product exposure for the Group-1 PK population in [Appendix 15, Figure 15.1.2.1.1](#) and [Figure 3](#). Geometric mean plasma nicotine concentrations up to 60 minutes following single use are shown by product exposure for the Group-1 PK population in [Appendix 15, Figure 15.1.2.1.1.1](#) and [Figure 4](#).

Figure 3 Geometric Mean Nicotine Plasma Concentration (ng/mL) on Single Use Days (Group-1 PK Population)



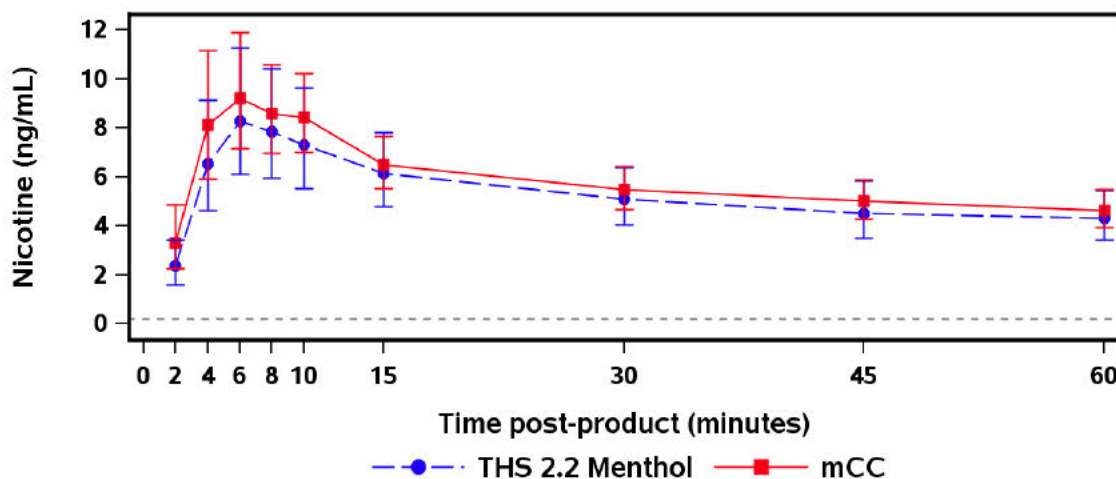
----- Lower limit of quantification (0.2 ng/mL)

Abbreviations: mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Figure 15.1.2.1.1](#).



Figure 4 Geometric Mean Nicotine Plasma Concentration (ng/mL) Time Profile from 0 to 60 Minutes Post-Product Use (Group-1 PK Population)



----- Lower limit of quantification (0.2 ng/mL)

Abbreviations: mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Figure 15.1.2.1.1.1](#).

The overall shape of the mean nicotine concentration-time curves was similar for THS 2.2 Menthol and mCC. The plasma concentration versus time profiles following single use of THS 2.2 Menthol and mCC were characterized by a rapid absorption phase, and after reaching C_{\max} at approximately the same time post-product use, the disposition of nicotine appeared to be biphasic (see semi-logarithmic plots in [Appendix 15, Figure 15.1.2.1.1](#) and [Figure 15.1.2.1.1.1](#)).

Plasma nicotine concentrations prior to T_0 were quantifiable ($>LLOQ$ of 0.2 ng/mL) for a number of subjects in the Group-1 PK population, with quantifiable plasma nicotine concentrations either observed on both Day 1 and Day 3, or Day 1 only (see [Appendix 15, Listing 15.3.3.2.1](#)). The numbers of subjects with quantifiable plasma nicotine concentrations prior to T_0 are summarized in [Table 14](#).

**Table 14 Summary of Subjects with Quantifiable Plasma Nicotine Concentration Prior to T₀ (Group-1 PK Population)**

	THS 2.2 Menthol - mCC (N=21)	mCC - THS 2.2 Menthol (N=22)	Group-1 PK (N=43)
Any plasma nicotine concentration >LLOQ prior to T ₀ , n (%)	15 (71.4%)	16 (72.7%)	31 (72.1%)
Plasma nicotine concentration prior to T ₀ , on Day 1 only, n (%)	10 (47.6%)	11 (50.0%)	21 (48.8%)
Plasma nicotine concentration prior to T ₀ , on Day 3 only, n (%)	0	0	0
Plasma nicotine concentration >LLOQ prior to T ₀ on both Day 1 and Day 3, n (%)	5 (23.8%)	5 (22.7%)	10 (23.3%)
Any plasma nicotine concentration prior to T ₀ which was >5% of C _{max} , n (%)	2 (9.5%)	5 (22.7%)	7 (16.3%)

Abbreviations: C_{max} = maximum plasma concentration; LLOQ = lower limit of quantification; mCC = menthol conventional cigarette; N = number of subjects; PK = pharmacokinetic; T₀ = time point of first product use during study day; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Listing 15.3.3.2.1](#).

The highest reported concentration prior to T₀ was 2.15 ng/mL. For all subjects who had nicotine concentrations prior to T₀ >LLOQ on both Day 1 and Day 3, the Day 3 value was lower than the Day 1 value and was generally close to the LLOQ.

11.1 Analysis of Primary Endpoints

The primary endpoint variables for this study were the nicotine PK parameters C_{max} and AUC_(0-last) following single use of THS 2.2 Menthol and mCC.

Subject listings of all single use nicotine PK parameters are provided in [Appendix 15, Listing 15.3.3.1](#) and are summarized for the Group-1 PK population by product exposure in [Appendix 15, Table 15.2.4.5](#) and [Table 15](#).

**Table 15 Summary of Nicotine Primary PK Parameters after Single Use (Group-1 PK Population)**

Pharmacokinetic Parameter (unit)	THS 2.2 Menthol (N=43)	mCC (N=43)
C_{max} (ng/mL)		
Number of subjects	43	43
Geometric mean	10.65	12.12
95% CI	7.99, 14.17	9.60, 15.30
Min, Max	0.4, 43.8	2.3, 58.1
CV (%)	117.10	87.71
AUC_(0-last) (ng.h/mL)		
Number of subjects	43	43
Geometric mean	23.84	24.50
95% CI	18.11, 31.39	19.61, 30.59
Min, Max	1.2, 117.7	4.9, 100.9
CV (%)	110.43	82.63

Abbreviations: AUC_(0-last) = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Table 15.2.4.5](#).

Three subjects had notably high C_{max} values following use of both products:

- Subject 0113; 38.1 ng/mL following THS 2.2 Menthol use on Day 1 and 34.2 ng/mL following mCC use on Day 3.
- Subject 0102; 32.2 ng/mL following mCC use on Day 1 and 34.8 ng/mL following THS 2.2 Menthol use on Day 3.
- Subject 0135; 58.1 ng/mL following mCC use on Day 1 and 43.8 ng/mL following THS 2.2 Menthol use on Day 3.

Five subjects had low C_{max} values following use of either THS 2.2 Menthol or mCC:

- Subject 0076; 2.6 ng/mL following mCC use on Day 3.
- Subject 0136; 2.3 ng/mL following mCC use on Day 3.
- Subject 0075; 1.4 ng/mL following THS 2.2 Menthol use on Day 3.
- Subject 0129; 0.4 ng/mL following THS 2.2 Menthol use on Day 3.
- Subject 0152; 2.6 ng/mL following mCC use on Day 1 and 1.0 ng/mL following THS 2.2 Menthol use on Day 3.



Three subjects had $AUC_{(0-last)}$ values >100 ng.h/mL:

- Subject 0084; 117.7 ng.h/mL following THS 2.2 Menthol use on Day 1.
- Subject 0102; 100.9 ng.h/mL following THS 2.2 Menthol use on Day 3.
- Subject 0140; 100.9 ng.h/mL following mCC use on Day 1.

The results of the statistical analyses of C_{max} and $AUC_{(0-last)}$ following single use are presented for the Group-1 PK population in [Appendix 15, Table 15.2.3.1](#) and in [Table 16](#).

Table 16 Analysis of Nicotine Primary PK Parameters after Single Use (Group-1 PK Population)

PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Means Ratio (THS 2.2 Menthol:mCC)				Precision (%)
			Geometric LS Mean	(%)	CV (%)	95% CI	
C_{max} (ng/mL)	THS 2.2	43	10.70				
	Menthol			88.47	63.54	68.64, 114.03	25.55
	mCC	43	12.09				
$AUC_{(0-last)}$ (ng.h/mL)	THS 2.2	43	23.99				
	Menthol			98.13	47.55	80.61, 119.46	21.33
	mCC	43	24.45				

Abbreviations: $AUC_{(0-last)}$ = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.

Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANOVA model. Geometrical CV% of the ratio is estimated only for the ratio. Precision is the largest difference between the 95% CI bounds and the mean.

Data Source: [Appendix 15, Table 15.2.3.1](#).

Following single use, there was no notable difference in the nicotine absorption between THS 2.2 Menthol and mCC as assessed by C_{max} and $AUC_{(0-last)}$, with the 95% CIs for both parameters spanning 100%.

High between-subject variability was noted for both C_{max} and $AUC_{(0-last)}$ for both products, with CV% values ranging from 87.71% to 117.10% and 82.63% to 110.43%, respectively ([Table 15](#)), with between-subject variability being higher following THS 2.2 Menthol use than mCC. The within-subject variability was high for both C_{max} (63.54%) and $AUC_{(0-last)}$ (47.55%).

The THS 2.2 Menthol:mCC ratio for $AUC_{(0-last)}$ was estimated with a precision of 21.33%, while the precision for C_{max} was 25.55%, with precision calculated as the largest difference between the 95% CI bounds and the mean.



The analysis approach recommended by the European Medicines Agency guideline on the investigation of bioequivalence [26] was performed in this study as a supportive analysis which excluded subjects with nicotine concentrations prior to T_0 which were greater than 5% of their respective C_{\max} values (Appendix 15, Table 15.2.4.3.2). As presented in Table 14, a total of 7 subjects were excluded from this supportive analysis (2 subjects in the THS 2.2 Menthol – mCC sequence and 5 subjects in the mCC – THS 2.2 Menthol sequence). The results from this supportive analysis were consistent with the original analysis, with geometric means ratios of 86.88% (95% CI: 65.11, 115.93) for C_{\max} and 99.22% (95% CI: 79.74, 123.45%) for $AUC_{(0-\text{last})}$. The THS 2.2 Menthol:mCC ratio for $AUC_{(0-\text{last})}$ was estimated with a precision of 24.23%, while the precision for C_{\max} was 29.05%.

Exploratory sub-group analyses were conducted for C_{\max} and $AUC_{(0-\text{last})}$ following single use in the following planned sub-groups: gender and ISO nicotine levels (≤ 0.6 mg and >0.6 to 1 mg). Nicotine PK parameters are summarized for the gender and ISO nicotine level sub-groups in Appendix 15, Table 15.2.4.5.1 and Table 15.2.4.5.2, respectively.

The results of the statistical analyses for the exploratory sub-groups are presented in Appendix 15, Table 15.2.3.2 and in Table 17.

**Table 17 Analysis of Nicotine Primary PK Parameters after Single Use by Sub-Group (Group-1 PK Population)**

			Geometric LS Means Ratio (THS 2.2 Menthol:mCC)			
PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Mean	CV (%)	95% CI	
C _{max} (ng/mL)						
Male	THS 2.2 Menthol mCC	23	10.70	97.20	56.20	70.47, 134.08
		23	11.01			
Female	THS 2.2 Menthol mCC	20	10.75	79.35	74.31	51.07, 123.28
		20	13.55			
ISO NL ≤0.6 mg	THS 2.2 Menthol mCC	25	14.13	118.30	37.83	95.49, 146.56
		25	11.95			
ISO NL >0.6 to ≤1 mg	THS 2.2 Menthol mCC	18	7.35	61.36	76.79	37.81, 99.57
		18	11.98			
AUC _(0-last) (ng.h/mL)						
Male	THS 2.2 Menthol mCC	23	26.26	91.01	40.11	71.79, 115.36
		23	28.85			
Female	THS 2.2 Menthol mCC	20	21.81	106.71	56.68	75.15, 151.53
		20	20.44			
ISO NL ≤0.6 mg	THS 2.2 Menthol mCC	25	27.87	129.13	33.08	106.92, 155.95
		25	21.58			
ISO NL >0.6 to ≤1 mg	THS 2.2 Menthol mCC	18	19.72	68.53	48.82	49.32, 95.21
		18	28.78			

Abbreviations: AUC_(0-last) = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; ISO = International Organization for Standardization; LS = least squares; mCC = conventional cigarette; NL = nicotine level; THS 2.2 = Tobacco Heating System 2.2.

Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANOVA model. Geometrical CV% of the ratio is estimated only for the ratio. Precision is the largest difference between the 95% CI bounds and the mean.

Data Source: [Appendix 15, Table 15.2.3.2.](#)

In female subjects, C_{max} was approximately 21% lower following THS 2.2 Menthol use compared to mCC use, although the 95% CIs spanned a broad range which included 100%, while C_{max} was comparable following THS 2.2 Menthol and mCC use for male



subjects. For $AUC_{(0-last)}$, there was no notable difference in the amount of nicotine absorbed for males or females between THS 2.2 Menthol and mCC use, with the 95% CIs spanning 100%.

For low nicotine level smokers, C_{max} and $AUC_{(0-last)}$ were approximately 18% and 29% higher, respectively, following THS 2.2 Menthol use compared to mCC, although the 95% CIs spanned 100% for C_{max} . For high nicotine level smokers, C_{max} and $AUC_{(0-last)}$ were approximately 39% and 31% lower, respectively, following THS 2.2 Menthol use compared to mCC, with the upper limit of the 95% CIs below 100% for both parameters.

11.2 Analysis of Secondary Endpoints

11.2.1 Pharmacokinetic Endpoints

11.2.1.1 Secondary Nicotine Parameters - THS 2.2 Menthol versus mCC

Subject listings of all single use nicotine PK parameters are provided in [Appendix 15, Listing 15.3.3.1](#). The secondary nicotine PK parameters are summarized for the Group-1 PK population by product exposure in [Appendix 15, Table 15.2.4.5](#) and [Table 18](#).

As per the SAP, the $t_{1/2}$ and $AUC_{(0-\infty)}$ were not reported because $t_{1/2}$ could not be reliably determined (R_{sq} adjusted <0.7) or could only be calculated over a period that was less than 1.5 half-lives for 5 subjects in the THS 2.2 Menthol – mCC sequence (all following THS 2.2 Menthol use) and for 4 subjects in the mCC – THS 2.2 Menthol sequence (1 subject following THS 2.2 menthol use and 3 subjects following mCC use) (see [Appendix 15, Listing 15.3.3.3](#)).

**Table 18 Summary of Nicotine Secondary PK Parameters after Single Use (Group-1 PK Population)**

Pharmacokinetic Parameter (unit)	THS 2.2 Menthol (N=43)	mCC (N=43)
AUC_(0-∞) (ng.h/mL)		
Number of subjects	37	40
Geometric mean	26.03	26.97
95% CI	20.32, 33.34	21.28, 34.17
Min, Max	5.7, 111.0	5.4, 117.1
CV (%)	85.72	85.42
t_{max} (min)		
Number of subjects	43	43
Median	6.00	6.00
Min, Max	4.0, 720.0	4.0, 30.0
AUC_(0-t') (ng.h/mL)		
Number of subjects	43	43
Geometric mean	0.59	0.80
95% CI	0.41, 0.84	0.61, 1.03
Min, Max	0.0, 4.7	0.1, 4.2
CV (%)	159.51	97.91
t_{1/2} (h)		
Number of subjects	37	40
Geometric mean	3.97	3.88
95% CI	3.25, 4.86	3.18, 4.72
Min, Max	1.3, 12.0	1.6, 11.5
CV (%)	65.91	67.53

Abbreviations: AUC_(0-∞) = area under plasma concentration-time curve from start of product use extrapolated to infinity; AUC_(0-t') = area under plasma concentration-time curve where t' is the subject-specific time of maximum nicotine concentration; CI = confidence interval; CV = coefficient of variation; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; t_{1/2} = terminal half-life; THS 2.2 = Tobacco Heating System 2.2; t_{max} = time to maximum plasma concentration.

Data Source: [Appendix 15, Table 15.2.4.5](#).

Two subjects had AUC_(0-∞) values >100 ng.h/mL:

- Subject 0102; 111.0 ng.h/mL following THS 2.2 Menthol use on Day 3.
- Subject 0140; 117.1 ng.h/mL following mCC use on Day 1.

Two subjects in the THS 2.2 Menthol – mCC sequence had abnormally long t_{max} values following THS 2.2 Menthol use on Day 1. Subjects 0084 and 0134 had PK profiles which had unexpectedly high nicotine concentration values at 720 minutes post-product use (10.6 and 5.76 ng/mL, respectively). The previous peak concentrations were observed at



15 minutes post-product use for Subjects 0084 and 0134 (7.99 and 4.65 ng/mL, respectively).

The results of the statistical analyses of secondary nicotine PK parameters following single use are presented for the Group-1 PK population in [Appendix 15, Table 15.2.4.1](#) and in [Table 19](#).

Table 19 Analysis of Nicotine Secondary PK Parameters after Single Use (Group-1 PK Population)

PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:mCC) (%)	CV (%)	95% CI
AUC _(0-∞) (ng.h/mL)	THS 2.2 Menthol	34	26.33	94.97	42.31	77.69, 116.09
	mCC	34	27.73			
AUC _(0-t') (ng.h/mL)	THS 2.2 Menthol	43	0.59	74.46	66.67	57.17, 96.98
	mCC	43	0.80			
t _{1/2} (h)	THS 2.2 Menthol	34	4.11	102.30	37.94	85.31, 122.66
	mCC	34	4.02			
PK Parameter (unit)	Product Exposure	Number of Subjects	Median	Median Difference		95% CI
t _{max} (minutes)	THS 2.2 Menthol	43	6.00	1.00		0.00, 2.50
	mCC	43	6.00			

Abbreviations: AUC_(0-∞) = area under plasma concentration-time curve from start of product use extrapolated to infinity; AUC_(0-t') = area under plasma concentration-time curve where t' is the subject-specific time of maximum nicotine concentration; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; t_{1/2} = terminal half-life; THS 2.2 = Tobacco Heating System 2.2; t_{max} = time to maximum plasma concentration.

Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANOVA model. Geometrical CV% of the ratio is estimated only for the ratio. For t_{max}, the median difference and its 95% CI are based on the Hodges-Lehmann method.

Data Source: [Appendix 15, Table 15.2.4.1](#).

There was no notable difference in the amount of nicotine absorbed as assessed by AUC_(0-∞) between THS 2.2 Menthol and mCC, with the 95% CIs spanning 100%. The amount of nicotine absorbed as assessed by AUC_(0-t') was approximately 26% lower following THS 2.2 Menthol use compared to mCC use (95% CI: 3.02, 42.83).

High between-subject variability was noted for both AUC_(0-∞) and AUC_(0-t') for both products, with CV% values ranging from 85.42% to 85.72% and 97.91% to 159.51%,



respectively (Table 18). The within-subject variability was high for both $AUC_{(0-\infty)}$ (42.31%) and $AUC_{(0-t)}$ (66.67%).

The $t_{1/2}$ was similar for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 4.11 hours (95% CI: 3.61, 4.68) and 4.02 hours (95% CI: 3.53, 4.57) for mCC, and a THS 2.2 Menthol:mCC ratio of 102.30% (95% CI: 85.31, 122.66).

For t_{max} , there was no notable difference between THS 2.2 Menthol and mCC, with a median value of 6 minutes for both products. The result of the bootstrapping analysis for t_{max} presented in Appendix 15, Table 15.2.4.3.1 was not consistent with the result presented in Table 19, and showed a longer t_{max} following THS 2.2 Menthol use (median value of 10.04 minutes) compared to mCC use (median value of 7.22 minutes) (LS mean ratio: 140.05%, 95% CI: 101.17, 199.83).

The results from the supportive analysis excluding subjects with nicotine concentrations prior to T_0 which were greater than 5% of their respective C_{max} values (Appendix 15, Table 15.2.4.3.2) were consistent with the original analysis, with geometric means ratios of 100.69% (95% CI: 80.47, 126.00) for $AUC_{(0-\infty)}$, 75.54% (95% CI: 55.63, 102.57) for $AUC_{(0-t)}$, 104.67% (95% CI: 85.25, 128.52) for $t_{1/2}$, and a median difference of 0.00 minutes (95% CI: -1.00, 1.00) for t_{max} .

For the male and female sub-populations, the amount of nicotine absorbed as assessed by $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ were consistent with the results of the whole Group-1 PK population. For both male and female subjects, there was no notable difference in $t_{1/2}$ and t_{max} for THS 2.2 Menthol compared to mCC (see Appendix 15, Table 15.2.4.5.1).

For the ISO nicotine level sub-populations, the amount of nicotine absorbed as assessed by $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ was comparable for low nicotine level smokers. For the high nicotine level smokers, the amount of nicotine absorbed as assessed by $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ was lower following THS 2.2 use compared to mCC use. There were no notable differences between THS 2.2 Menthol and mCC in mean $t_{1/2}$ and median t_{max} values (see Appendix 15, Table 15.2.4.5.2).

11.2.1.2 Nicotine Pharmacokinetic Endpoints Following Single Use of THS 2.2 Menthol and NRT Gum.

Plasma nicotine concentrations (ng/mL) following single uses of THS 2.2 Menthol and NRT gum, and the nominal and actual times of PK blood sample collection are listed by subject in Appendix 15, Listing 15.3.3.2. Plasma nicotine concentrations are summarized for the Group-2 PK population by each scheduled time point in Appendix 15, Table 15.2.4.6.

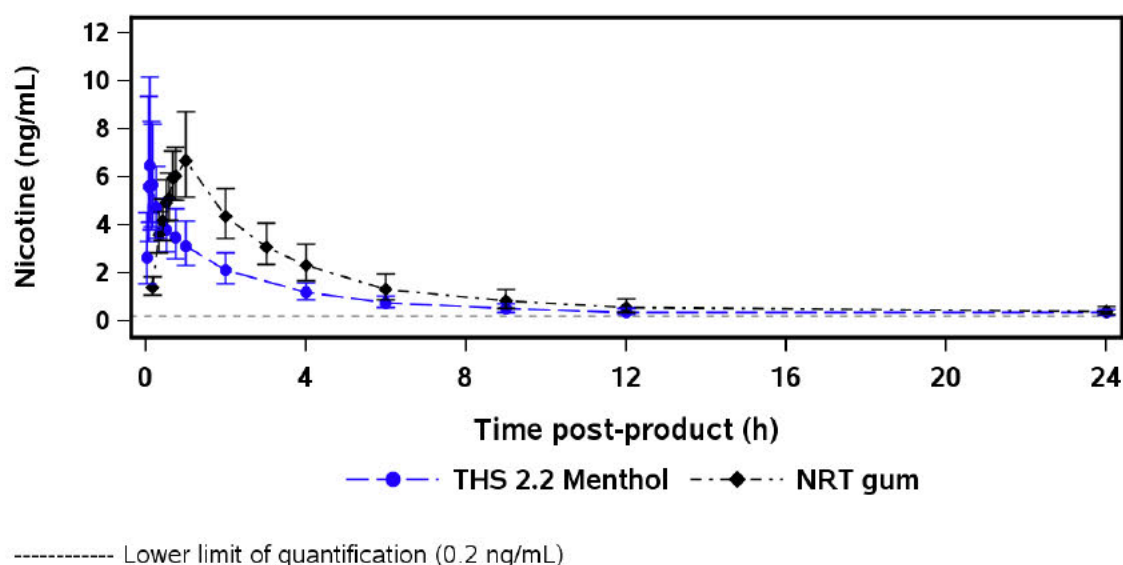
Plasma nicotine concentration profiles for all subjects following single use of THS 2.2 Menthol and NRT gum are shown for the Group-2 PK population in Appendix 15,



Figure 15.1.2.2.2 (linear and semi-logarithmic scales). Plasma nicotine concentration profiles by individual subject following single use of THS 2.2 and NRT gum are shown for the PK population in Appendix 15, Figure 15.1.2.3 (linear and semi-logarithmic scales).

Geometric mean nicotine plasma concentration-time profiles following single use are shown by product exposure for the Group-2 PK population in Appendix 15, Figure 15.1.2.1.2 and Figure 5. Geometric mean plasma nicotine concentrations up to 60 minutes following single use are shown by product exposure for the Group-2 PK population in Appendix 15, Figure 15.1.2.1.2.1 and Figure 6.

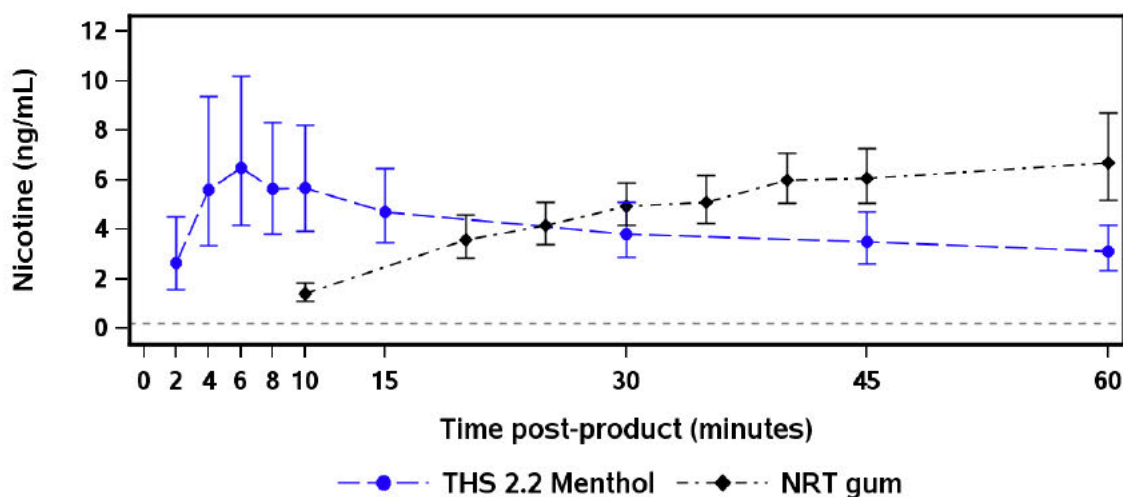
Figure 5 Geometric Mean Nicotine Plasma Concentrations (ng/mL) on Single Use Days (Group-2 PK Population)



Abbreviations: NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.
Data Source: Appendix 15, Figure 15.1.2.1.2.



Figure 6 Geometric Mean Nicotine Plasma Concentrations (ng/mL) Time Profile from 0 to 60 Minutes Post-Product Use (Group-2 PK Population)



----- Lower limit of quantification (0.2 ng/mL)

Abbreviations: NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.
Data Source: [Appendix 15, Figure 15.1.2.1.2.1](#).

The overall shape of the mean nicotine concentration-time curves was different for THS 2.2 menthol and NRT gum. The plasma concentration versus time profile following single use was characterized by a rapid absorption phase for THS 2.2 Menthol, while C_{\max} was comparable but attained later following NRT gum use. After reaching C_{\max} , the disposition of nicotine appeared to be biphasic for both products (see semi-logarithmic plots in [Appendix 15, Figure 15.1.2.1.2](#) and [Figure 15.1.2.1.2.1](#)).

Plasma nicotine concentrations prior to T_0 were quantifiable ($>LLOQ$ of 0.2 ng/mL) for a number of subjects in the Group-2 PK population, with quantifiable plasma nicotine concentrations either observed on both Day 1 and Day 3, or Day 1 only (see [Appendix 15, Listing 15.3.3.2.1](#)). The only exception was Subject 0051 (THS 2.2 Menthol – NRT gum) who had a quantifiable plasma nicotine concentration, prior to T_0 , on Day 3. The numbers of subjects with quantifiable plasma nicotine concentrations prior to T_0 are summarized in [Table 20](#).

**Table 20 Summary of Subjects with Quantifiable Nicotine Plasma Concentration Prior to T₀ (Group-2 PK Population)**

	THS 2.2 Menthol – NRT gum (N=9)	NRT gum – THS 2.2 Menthol (N=9)	Group-2 PK (N=18)
Any plasma nicotine concentration >LLOQ prior to T ₀ , n (%)	5 (55.6%)	8 (88.9%)	13 (72.2%)
Plasma nicotine concentration prior to T ₀ , on Day 1 only, n (%)	2 (22.2%)	6 (66.7%)	8 (44.4%)
Plasma nicotine concentration prior to T ₀ , on Day 3 only, n (%)	1 (11.1%)	0	1 (5.6%)
Plasma nicotine concentration >LLOQ prior to T ₀ on both Day 1 and Day 3, n (%)	2 (22.2%)	2 (22.2%)	4 (22.2%)
Any plasma nicotine concentration prior to T ₀ which was >5% of C _{max} , n (%)	1 (11.1%)	4 (44.4%)	5 (27.8%)

Abbreviations: C_{max} = maximum plasma concentration; LLOQ = lower limit of quantification; N = number of subjects; NRT gum = nicotine replacement therapy gum; PK = pharmacokinetic; T₀ = time point of first product use during study day; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Listing 15.3.3.2.1](#).

The highest reported concentration prior to T₀ was 0.922 ng/mL. For most subjects who had nicotine concentrations prior to T₀ >LLOQ on both Day 1 and Day 3, the Day 3 value was lower than the Day 1 value and was generally close to the LLOQ.

Subject listings of all single use nicotine PK parameters are provided in [Appendix 15, Listing 15.3.3.1](#). The nicotine PK parameters are summarized for the Group-2 PK population by product exposure in [Appendix 15, Table 15.2.4.5](#) and [Table 21](#).

As per the SAP, t_{1/2} and AUC_(0-∞) were not reported for 2 subjects in the THS 2.2 Menthol – NRT gum sequence and 1 subject in the NRT gum – THS 2.2 Menthol sequence because t_{1/2} could not be reliably determined (Rs_q adjusted <0.7) (2 subjects following THS 2.2 Menthol use and 1 subject following NRT gum use).

**Table 21 Summary of Nicotine PK Parameters after Single Use (Group-2 PK Population)**

Pharmacokinetic Parameter (unit)	THS 2.2 Menthol (N=18)	NRT Gum (N=18)
C_{max} (ng/mL)		
Number of subjects	18	18
Geometric mean	7.64	7.52
95% CI	4.92, 11.85	5.81, 9.72
Min, Max	1.3, 45.8	2.7, 34.1
CV (%)	108.56	55.24
AUC_(0-last) (ng.h/mL)		
Number of subjects	18	18
Geometric mean	15.61	27.94
95% CI	11.09, 21.96	20.23, 38.57
Min, Max	3.9, 48.3	9.6, 86.4
CV (%)	77.53	72.31
AUC_(0-∞) (ng.h/mL)		
Number of subjects	16	17
Geometric mean	16.78	29.71
95% CI	11.69, 24.08	21.08, 41.87
Min, Max	4.9, 53.3	11.0, 91.7
CV (%)	76.36	74.88
t_{max} (min)		
Number of subjects	18	18
Median	8.00	45.00
Min, Max	4.0, 30.0	25.0, 60.0
AUC_(0-t) (ng.h/mL)		
Number of subjects	18	18
Geometric mean	3.38	2.97
95% CI	2.41, 4.72	2.34, 3.78
Min, Max	1.0, 11.2	1.1, 7.6
CV (%)	75.49	50.66

**Table 21 Summary of Nicotine PK Parameters after Single Use (Group-2 PK Population) (continued)**

Pharmacokinetic parameter (unit)	THS 2.2 Menthol (N=18)	NRT gum (N=18)
t_{1/2} (h)		
Number of subjects	16	17
Geometric mean	3.34	3.82
95% CI	2.45, 4.57	2.79, 5.22
Min, Max	1.3, 7.7	1.3, 11.6
CV (%)	63.71	66.59

Abbreviations: AUC_(0-last) = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; AUC_(0-∞) = area under plasma concentration-time curve from start of product use extrapolated to infinity; AUC_(0-t') = area under plasma concentration-time curve where t' is the subject-specific time of maximum nicotine concentration; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2; t_{1/2} = terminal half-life; t_{max} = time to maximum plasma concentration.

Data Source: [Appendix 15, Table 15.2.4.5](#).

The results of the statistical analyses of nicotine PK parameters following single use are presented for the Group-2 PK population in [Appendix 15, Table 15.2.4.2](#) and in [Table 22](#).

**Table 22 Analysis of Nicotine PK Parameters after Single Use (Group-2 PK Population)**

PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:NRT gum)		CV (%)	95% CI	P-value (1-sided)
					(%)			
C_{\max} (ng/mL)	THS 2.2 Menthol	18	7.64	101.63	78.75	62.21, 166.04	0.473	
	NRT gum	18	7.52					
$AUC_{(0-\text{last})}$ (ng.h/mL)	THS 2.2 Menthol	18	15.61	55.87	57.19	38.36, 81.36	0.998	
	NRT gum	18	27.94					
$AUC_{(0-\infty)}$ (ng.h/mL)	THS 2.2 Menthol	15	15.77	50.72	51.05	34.66, 74.21	0.999	
	NRT gum	15	31.09					
$AUC_{(0-t')}$ (ng.h/mL)	THS 2.2 Menthol	18	3.38	113.63	54.10	79.43, 162.55	0.230	
	NRT gum	18	2.97					
$t_{1/2}$ (h)	THS 2.2 Menthol	15	3.20	92.06	28.97	73.55, 115.22		
	NRT gum	15	3.47					
PK Parameter (unit)	Product Exposure	Number of Subjects	Median	Median Difference		95% CI	P-value (1-sided)	
t_{\max} (minutes)	THS 2.2 Menthol	18	8.00	-37.50		-45.00, -31.50	<0.001	
	NRT gum	18	45.00					

Abbreviations: $AUC_{(0-\infty)}$ = area under plasma concentration-time curve from start of product use extrapolated to infinity; $AUC_{(0-\text{last})}$ = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; $AUC_{(0-t')}$ = area under plasma concentration-time curve where t' is the subject-specific time of maximum nicotine concentration; CI = confidence interval; C_{\max} = maximum plasma concentration; CV = coefficient of variation; LS = least squares; Max = maximum; Min = minimum; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2; $t_{1/2}$ = terminal half-life; t_{\max} = time to maximum plasma concentration.

Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANOVA model. Geometrical CV% of the ratio is estimated only for the ratio. For t_{\max} , the median difference and its 95% CI are based on the Hodges-Lehmann method.

Data Source: [Appendix 15, Table 15.2.4.2.](#)



Following single use, there was no statistically significant difference in the amount of nicotine absorbed as assessed by C_{\max} between THS 2.2 Menthol and NRT gum, with the 95% CIs spanning 100%. The amount of nicotine absorbed as assessed by $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ were approximately 44% and 49% lower, respectively, for THS 2.2 Menthol compared to NRT gum (P values were 0.998 and 0.999, respectively, for the one-sided tests that the exposure was greater for THS 2.2 Menthol compared to NRT gum). The results obtained for C_{\max} and $AUC_{(0-\text{last})}$ do not support the study hypotheses for these 2 parameters (see [Section 8.3.1](#)). The amount of nicotine absorbed as assessed by $AUC_{(0-t)}$ was higher (1.13-fold) for THS 2.2 Menthol compared to NRT gum, although a significant difference could not be detected ($P = 0.230$).

High between-subject variability was reported for C_{\max} , $AUC_{(0-\text{last})}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ for both THS 2.2 Menthol and NRT gum, with CV% values ranging from 75.49% to 108.56% for THS 2.2 Menthol and 50.66% to 74.88% for NRT gum. The within-subject variability was high for C_{\max} , $AUC_{(0-\text{last})}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ (51.05% to 78.75%).

The $t_{1/2}$ was comparable between the 2 products, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 3.20 hours (95% CI: 2.72, 3.75) and 3.47 hours (95% CI: 2.96, 4.08) for NRT gum and a THS 2.2 Menthol:NRT gum ratio of 92.06% (95% CI: 73.55, 115.22).

The t_{\max} was significantly shorter for THS 2.2 Menthol (8 minutes) than for NRT gum (45 minutes) which is approximately 2 minutes longer than observed in the Group-1 PK population following THS 2.2 Menthol use and supports the study hypothesis concerning t_{\max} (see [Section 8.3.1](#)). The result of the bootstrapping analysis presented in [Appendix 15, Table 15.2.4.3.1](#) was also consistent with the result presented in [Table 22](#).

A supportive analysis was conducted in the Group-2 PK population which excluded subjects with nicotine concentrations prior to T_0 greater than 5% of their respective C_{\max} values ([Appendix 15, Table 15.2.4.3.2](#)). As presented in [Table 20](#), a total of 5 subjects were excluded from this supportive analysis (1 subject in the THS 2.2 – NRT gum sequence and 4 subjects in the NRT gum – THS 2.2 group). The results were consistent with those reported for the main analysis for the Group-2 PK population.

For the sub-populations, the THS 2.2 Menthol effect estimates were highly variable due to the limited number of subjects in each stratum ($N=6$ to 10). The C_{\max} was higher for males and high nicotine level smokers following THS 2.2 Menthol use compared to NRT gum but was lower for females and low nicotine level smokers. The amount of nicotine absorbed as assessed by $AUC_{(0-\text{last})}$ and $AUC_{(0-\infty)}$ was lower for both genders and high and low nicotine level smokers following THS 2.2 Menthol use compared to NRT gum. However, for females and low nicotine level smokers, exposure was consistently lower (approximately 54% to 62%) following THS 2.2 Menthol use compared to NRT gum than the decrease in exposure observed in males and high nicotine level smokers (approximately 15% to 27%). The amount of nicotine absorbed as assessed by $AUC_{(0-t)}$



was higher for males and high nicotine level smokers following THS 2.2 Menthol use compared to NRT gum but was lower for females and low nicotine level smokers (see [Appendix 15, Table 15.2.4.5.1](#) and [Table 15.2.4.5.2](#)).

11.2.2 Subjective Effects of Smoking Endpoints

11.2.2.1 Urge-to-Smoke Symptoms (QSU-brief)

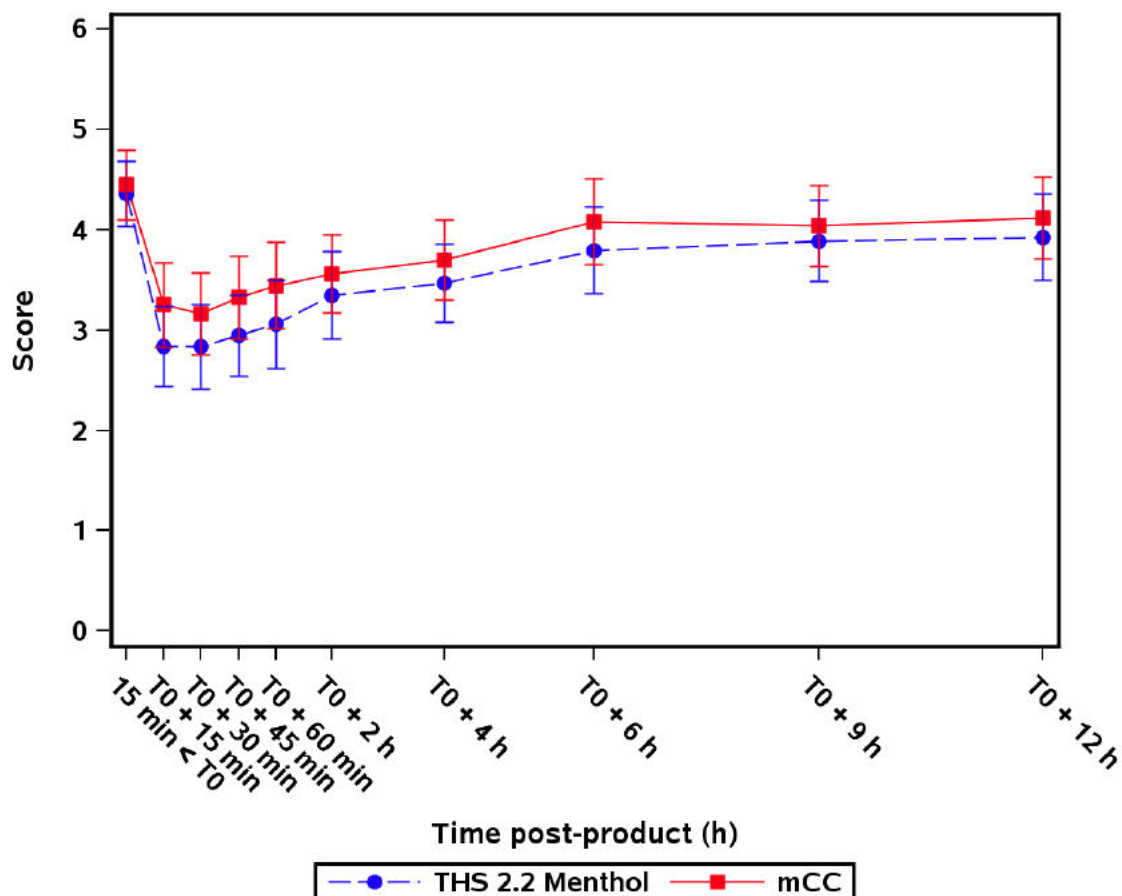
Responses to the QSU-brief questionnaire used to measure urge-to-smoke symptoms on single use days, factor scores (Factor 1 reflecting the desire and intention to smoke with smoking perceived as rewarding and Factor 2 reflecting anticipation of relief from negative effects of not smoking), and total scores are listed by subject in [Appendix 15, Listing 15.3.6.11](#) and are summarized for the Group-1 and Group-2 PK populations in [Appendix 15, Table 15.2.4.14](#). For further details of the QSU-brief questionnaire and derivation of the factor and total scores, see [Section 9.7.1.7.1](#).

11.2.2.1.1 THS 2.2 Menthol versus mCC

Line graphs showing the mean scores for the QSU-brief over time following single product use are presented for the Group-1 PK population in [Appendix 15, Figure 15.1.2.10.1](#) (Factor 1, Factor 2, and total scores) and in [Figure 7](#) (total score).



Figure 7 Mean Total Scores for QSU-Brief During Single Use (Group-1 PK Population)



Abbreviations: mCC = conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.
QSU-brief scores reported on a 7-point scale. Higher values indicate greater intensity of urge.
Data Source: [Appendix 15, Figure 15.1.2.10.1](#).

The overall shape of the mean total score versus time curves was similar following THS 2.2 Menthol and mCC use, however, the urge-to-smoke was lower throughout the assessment period following THS 2.2 Menthol use compared to mCC use.

The average urge-to-smoke total scores were 4.36 for THS 2.2 Menthol and 4.45 for mCC at 15 minutes < T₀. For THS 2.2, the average urge-to-smoke total score dropped by a maximum of approximately 35% at T₀ + 15 minutes following single use. For mCC, the decrease in total score was 27% at T₀ + 15 minutes, with the maximum decrease of 29% achieved at T₀ + 30 minutes. These reductions corresponded to 1.52 and 1.28 point maximum decreases from baseline for THS 2.2 Menthol and mCC use, respectively.



For both THS 2.2 Menthol and mCC, the average total score had not returned to baseline values by the last assessment time point at 12 hours post-product use (90% and 93% of baseline, respectively), with the urge to smoke being strongest at $T_0 + 12$ hours.

For the sub-populations, the trend in average urge-to-smoke factors and total score for male and female subjects was consistent with that of the whole Group-1 PK population, with no gender differences observed.

For the ISO nicotine level sub-populations, average urge-to-smoke factors and total score were lower for the low nicotine level smokers following THS 2.2 Menthol use compared to mCC use. Factor and total scores were similar following THS 2.2 Menthol and mCC use for high nicotine level smokers.

The results from the statistical analysis of the QSU-brief questionnaire factors and total score mean over all time points are presented in [Appendix 15, Table 15.2.4.12](#) and [Table 23](#). Profiles of the LS mean differences (THS 2.2 Menthol – mCC) over time are presented for the Group-1 PK population in [Appendix 15, Figure 15.1.2.11.1](#) (Factor 1, Factor 2, and total scores).

Table 23 Analysis of QSU-brief Questionnaire Factors and Total Score (Group-1 PK Population)

Score	Product Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 Menthol – mCC)		
				LS Mean	SE	95% CI
Factor 1	THS 2.2 Menthol	43	4.14	-0.32	0.292	-0.90, 0.26
	mCC	43	4.46			
Factor 2	THS 2.2 Menthol	43	2.56	-0.24	0.279	-0.80, 0.31
	mCC	43	2.80			
Total	THS 2.2 Menthol	43	3.36	-0.28	0.255	-0.79, 0.22
	mCC	43	3.64			

Abbreviations: CI = confidence interval; LS = least squares; mCC = conventional cigarette; SE = standard error; THS 2.2 = Tobacco Heating System 2.2.

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: [Appendix 15, Table 15.2.4.12](#).

There was no notable difference in QSU-brief total for THS 2.2 Menthol compared to mCC, with an LS mean difference over all time points of -0.28 points for THS 2.2 Menthol - mCC following single use (95% CI: -0.79, 0.22). Consistent results were obtained for the 2 factors; Factor 1 THS 2.2 Menthol - mCC difference of -0.32 (95% CI: -0.90, 0.26); and Factor 2 THS 2.2 Menthol - mCC difference of -0.24 (95% CI: -0.80, 0.31).



The LS mean differences between THS 2.2 Menthol and mCC for the total score, Factor 1, and Factor 2 scores were comparable throughout, and there were no notable differences at any time point. The difference between THS 2.2 Menthol and mCC for the total score was greatest at $T_0 + 15$ minutes with a THS 2.2 Menthol - mCC difference of -0.41 (95% CI -1.14, 0.31).

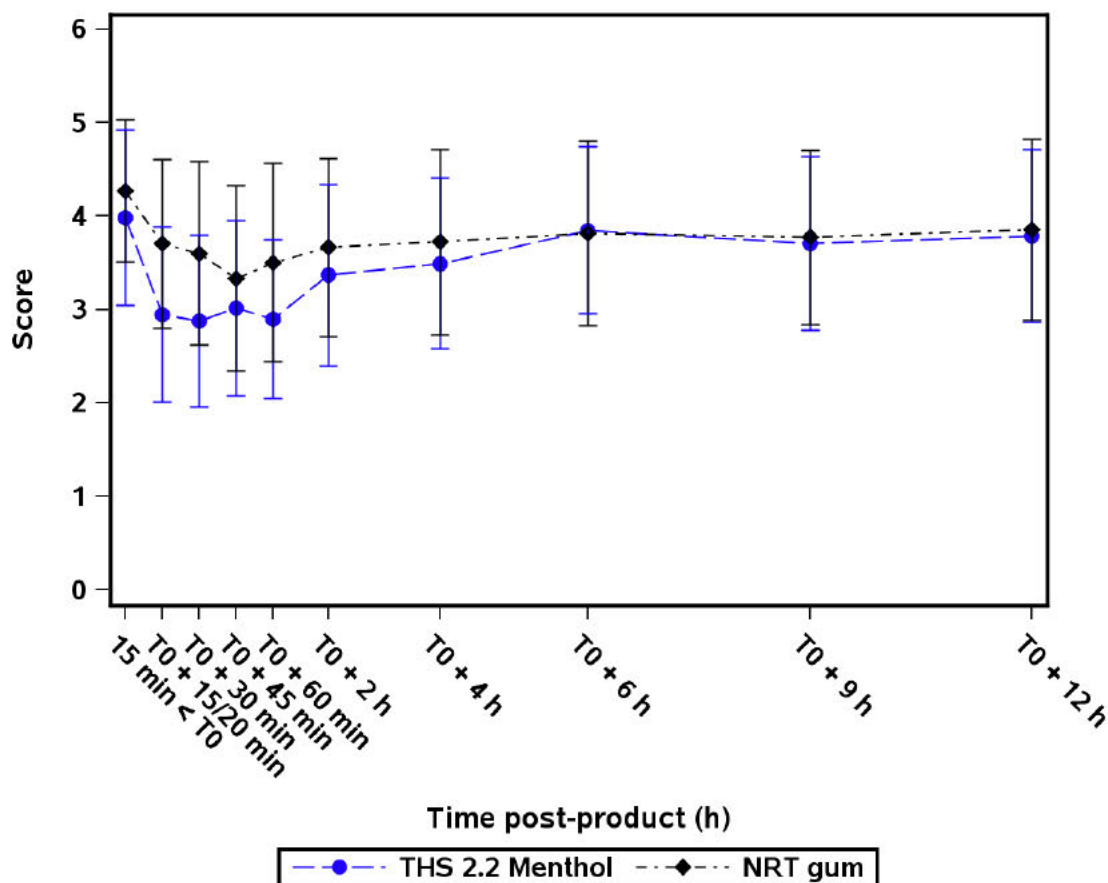
The results for the QSU-brief bootstrapping analysis presented in [Appendix 15, Table 15.2.4.13](#) showed differences between THS 2.2 Menthol and mCC use which were consistent with the results presented in [Table 23](#), however the upper limit of the 95% CIs for the total score and Factor 1 were less than 0.

11.2.2.1.2 THS 2.2 Menthol versus NRT Gum

Line graphs showing the mean scores for the QSU-brief over time following single product use are presented for the Group-2 PK population in [Appendix 15, Figure 15.1.2.10.2](#) (Factor 1, Factor 2, and total scores) and in [Figure 8](#) (total score).



Figure 8 Mean Total Scores for QSU-Brief During Single Use (Group-2 PK Population)



Abbreviations: NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2. QSU-brief scores reported on a 7-point scale. Higher values indicate greater intensity of urge. Data Source: [Appendix 15, Figure 15.1.2.10.2](#).

The overall shape of the mean total score versus time curves was different following THS 2.2 Menthol and NRT gum use. THS 2.2 Menthol use decreased the urge-to-smoke more than NRT gum use, particularly for the first 4 hours post-product use.

The average urge-to-smoke total scores were 3.98 for THS 2.2 Menthol and 4.27 for NRT gum at 15 minutes <T₀. For THS 2.2 Menthol, the average urge-to-smoke total score decreased from baseline by approximately 26% at T₀ + 15 minutes to a maximum of 28% at T₀ + 30 minutes following single use. For NRT gum, the decrease in total score was less pronounced with the maximum decrease taking longer to achieve (approximate 13% decrease at T₀ + 20 minutes to an approximate 22% decrease at T₀ + 45 minutes). The maximum reductions corresponded to 1.10 and 0.94 point decreases from baseline for THS 2.2 Menthol and NRT gum use, respectively. Both total scores were below their



respective baseline values at 12 hours post-product use (95% and 90% for THS 2.2 Menthol and NRT gum, respectively).

For the sub-populations (male and female subjects, low and high nicotine levels), the trends observed were consistent with those of the whole Group-2 PK population.

The results from the statistical analysis of the QSU-brief questionnaire factors and total score mean over all time points are presented in [Appendix 15, Table 15.2.4.12](#) and [Table 24](#) (overall time point). Profiles of the LS mean differences (THS 2.2 Menthol – NRT gum) over time are presented for the Group-2 PK population in [Appendix 15, Figure 15.1.2.11.2](#) (Factor 1, Factor 2, and total scores).

Table 24 Analysis of QSU-brief Questionnaire Factors and Total Score (Group-2 PK Population)

Score	Product Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 Menthol – NRT Gum)		
				LS Mean	SE	95% CI
Factor 1	THS 2.2 Menthol	18	4.09	-0.29	0.364	-1.01, 0.43
	NRT gum	18	4.38			
Factor 2	THS 2.2 Menthol	18	2.56	-0.38	0.165	-0.71, -0.05
	NRT gum	18	2.95			
Total	THS 2.2 Menthol	18	3.33	-0.34	0.267	-0.87, 0.19
	NRT gum	18	3.66			

Abbreviations: CI = confidence interval; LS = least squares; NRT gum = nicotine replacement therapy gum; SE = standard error; THS 2.2 = Tobacco Heating System 2.2.

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: [Appendix 15, Table 15.2.4.12](#).

There was no notable difference in QSU-brief total score for THS 2.2 Menthol compared to NRT gum, with an LS mean difference over all time points of -0.34 points for THS 2.2 Menthol – NRT gum following single use (95% CI: -0.87, 0.19). Consistent results were obtained for Factor 1, with a THS 2.2 Menthol - NRT gum difference of -0.29; (95% CI: -1.01, 0.43). Overall results for Factor 2 were also similar, with a THS 2.2 Menthol - NRT gum difference of -0.38, although the upper limit of the 95% CIs was below 0 (95% CI: -0.71, -0.05).

The differences between THS 2.2 Menthol and NRT gum for the total score and Factor 1 were greatest at $T_0 + 15/20$ minutes (THS 2.2 Menthol - NRT gum difference of -0.76 points; 95% CI: -1.65, 0.12).

The results for the QSU-brief bootstrapping analysis presented in [Appendix 15, Table 15.2.4.13](#) were consistent with the results presented in [Table 24](#).



11.2.2.2 Modified Cigarette Evaluation Questionnaire

Responses to the individual items of the MCEQ used to assess product evaluation and the subscale scores for the MCEQ are listed in [Appendix 15, Listing 15.3.6.12](#). The subscale scores for the MCEQ following single use are summarized for the Group-1 PK population in [Appendix 15, Table 15.2.4.17](#). For further details of the MCEQ, see [Section 9.7.1.7.2](#).

The results from the statistical analysis of the MCEQ subscales score are presented in [Appendix 15, Table 15.2.4.15](#) and [Table 25](#).

Table 25 Analysis of MCEQ Subscales (Group-1 PK Population)

Subscale	Product Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 Menthol – mCC)		
				LS Mean	SE	95% CI
Aversion	THS 2.2 Menthol	43	2.37	-0.10	0.248	-0.60, 0.41
	mCC	43	2.46			
Craving reduction	THS 2.2 Menthol	43	3.30	-0.14	0.196	-0.54, 0.26
	mCC	43	3.44			
Enjoyment of respiratory tract sensation	THS 2.2 Menthol	43	3.34	-0.59	0.223	-1.05, -0.14
	mCC	43	3.94			
Psychological reward	THS 2.2 Menthol	43	2.77	-0.19	0.105	-0.40, 0.03
	mCC	43	2.96			
Smoking satisfaction	THS 2.2 Menthol	43	3.19	-1.12	0.198	-1.53, -0.72
	mCC	43	4.31			

Abbreviations: CI = confidence interval; LS = least squares; mCC = conventional cigarette; SE = standard error; THS 2.2 = Tobacco Heating System 2.2.

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: [Appendix 15, Table 15.2.4.15](#).

Based on the results from the product comparison using the MCEQ subscale scores following single use, differences were observed for two subscales, with enjoyment of respiratory tract sensation being 0.59 points (95% CI: 0.14, 1.05) lower and smoking satisfaction being 1.12 points (95% CI: 0.72, 1.53) lower for THS 2.2 Menthol compared to mCC.

There was no notable difference in aversion, craving reduction, and psychological reward between THS 2.2 Menthol and mCC following single use, with aversion being 0.10 points (95% CI: -0.41, 0.60) lower, craving reduction being 0.14 points (95% CI: -0.26, 0.54)



lower, and psychological reward being 0.19 points lower (95% CI: -0.03, 0.40) for THS 2.2 Menthol than mCC.

The results for the MCEQ bootstrapping analysis presented in [Appendix 15, Table 15.2.4.16](#) were consistent with the results presented in [Table 25](#).

For the sub-populations, enjoyment of respiratory tract sensation was lower for female subjects for THS 2.2 Menthol compared to mCC while scores were similar for the 2 products for male subjects. All other results were consistent with those of the whole Group-1 PK population.

For the ISO nicotine level sub-populations, aversion was higher for THS 2.2 Menthol use compared to mCC for the low nicotine level smokers but was lower for THS 2.2 Menthol use compared to mCC for the high nicotine level smokers. All other results were consistent with those of the whole Group-1 PK population.

11.2.3 Biomarker Endpoints

11.2.3.1 Blood COHb

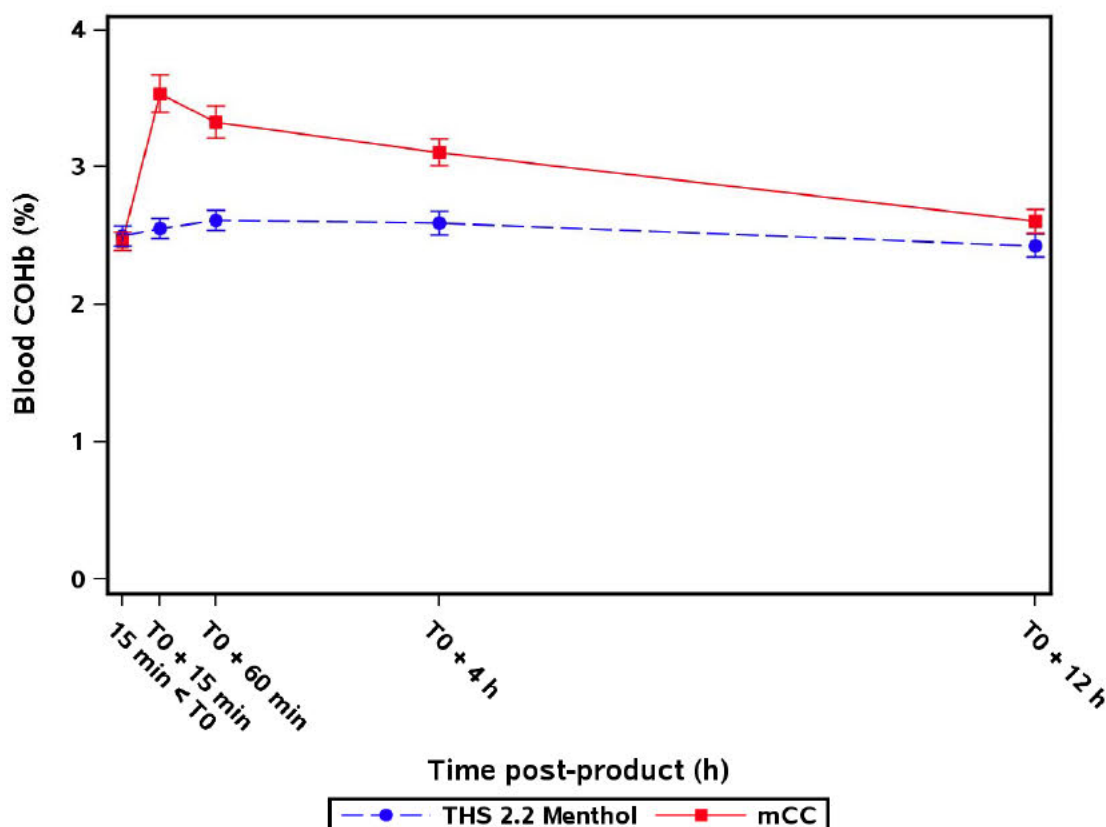
The levels of blood COHb (%) and the timing of the COHb assessments following single use are presented by subject in [Appendix 15, Listing 15.3.3.4](#). Levels of COHb are summarized for the Group-1 and Group-2 PK populations in [Appendix 15, Table 15.2.4.8.1](#) and the number of subjects with COHb levels $\leq 2\%$ and $> 2\%$ are summarized for each measurement in [Appendix 15, Table 15.2.4.8.2](#).

11.2.3.1.1 THS 2.2 Menthol versus mCC

A line graph showing mean COHb levels by product exposure over time following single use for the Group-1 PK population is presented in [Appendix 15, Figure 15.1.2.6.1](#) and in [Figure 9](#).



Figure 9 Mean Blood COHb (%) on Single Use Days (Group-1 PK Population)



Abbreviations: COHb = carboxyhemoglobin; mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Figure 15.1.2.6.1.](#)

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.50% for THS 2.2 Menthol and 2.46% for mCC, with a comparable range of values for each product prior to use (2.1% to 3.1% for THS 2.2 and 2.2% to 3.1% for mCC).

At $T_0 + 15$ minutes, the mean COHb value had increased to a maximum of 3.53% for mCC, while COHb remained steady at 2.55% and remained stable for the 12 hour post-product evaluation period for THS 2.2 Menthol users (within the range of 2.42% to 2.61%, with the maximum achieved at $T_0 + 60$ minutes). At $T_0 + 12$ hours, COHb values were similar to baseline for both THS 2.2 Menthol and mCC users.

The results from the statistical analysis of the COHb levels on single use days are presented in [Appendix 15, Table 15.2.4.7](#) and [Table 26](#). A profile of the LS mean ratio



(THS 2.2 Menthol:mCC) over time is presented for the Group-1 PK population in [Appendix 15, Figure 15.1.2.7.1](#).

Table 26 Analysis of Blood COHb (Group-1 PK Population)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2 Menthol:mCC) (%)	CV (%)	95% CI
THS 2.2 Menthol	43	2.54			
mCC	43	3.12	81.47	12.68	78.95, 84.07

Abbreviations: CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.

Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANOVA model.

Geometrical CV% of the ratio is estimated only for the ratio.

Data Source: [Appendix 15, Table 15.2.4.7](#).

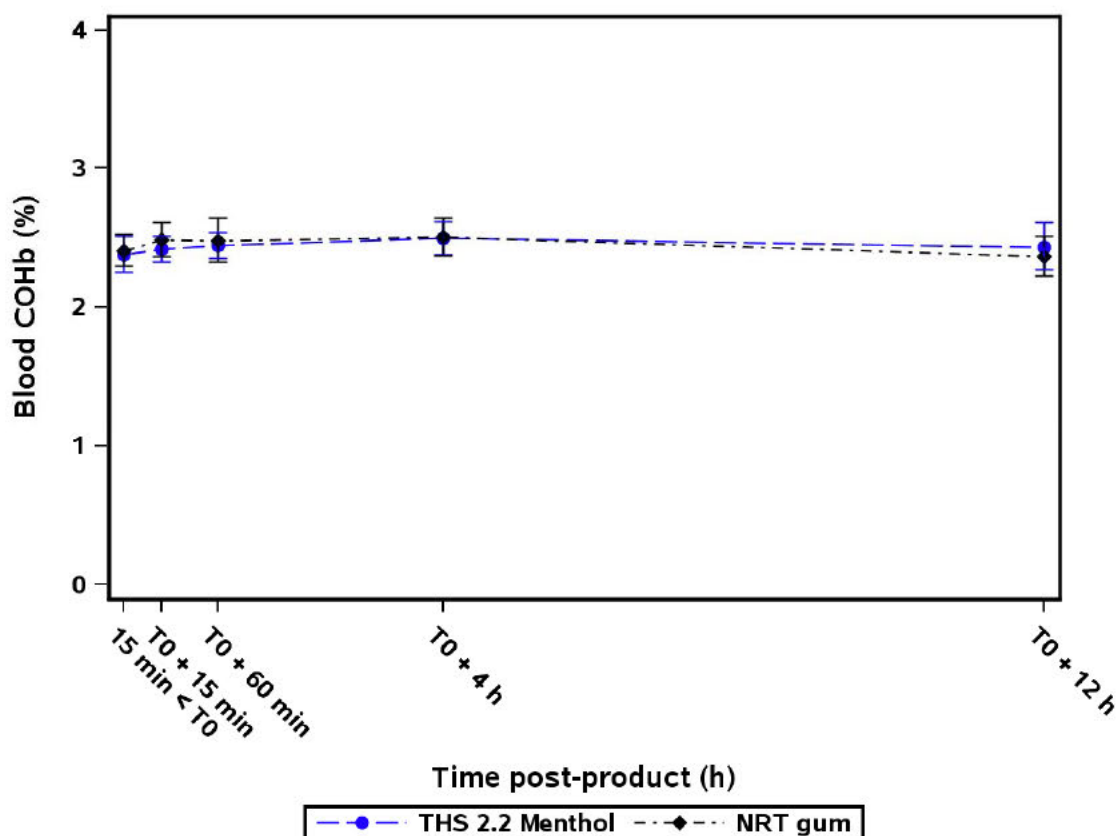
Across the full 12 hour post-product evaluation period, the THS 2.2 Menthol:mCC ratio for COHb was 81.47% (95% CI: 78.95, 84.07) after single use. Furthermore, the THS 2.2 Menthol:mCC ratio results showed COHb levels to be lower following THS 2.2 Menthol use compared to mCC use at all individual time points.

11.2.3.1.2 THS 2.2 Menthol versus NRT Gum

A line graph showing mean COHb levels by product exposure over time following single use for the Group-2 PK population is presented in [Appendix 15, Figure 15.1.2.6.2](#) and in [Figure 10](#).



Figure 10 Mean Blood COHb (%) on Single Use Days (Group-2 PK Population)



Abbreviations: COHb = carboxyhemoglobin; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Figure 15.1.2.6.2.](#)

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.38% for THS 2.2 Menthol and 2.41% for NRT gum with a comparable range of values for each product prior to use (2.0% to 2.8% for THS 2.2 Menthol and 2.0% to 3.0% for NRT gum). Mean COHb levels remained relatively unchanged throughout the assessment day (2.42% to 2.49% for THS 2.2 Menthol and 2.36% to 2.50% for NRT gum), with the maximum COHb value achieved at T₀ + 4 hours for both products.

The results from the statistical analysis of the COHb levels on single use days are presented in [Appendix 15, Table 15.2.4.7](#) and [Table 27](#). A profile of the LS mean ratio (THS 2.2 Menthol:NRT gum) over time is presented for the Group-2 PK population in [Appendix 15, Figure 15.1.2.7.2.](#)

**Table 27 Analysis of Blood COHb (Group-2 PK Population)**

Product Exposure	Number of Subjects	Geometric LS Mean Ratio (THS 2.2 Menthol:NRT Gum)		CV (%)	95% CI
		LS Mean	(%)		
THS 2.2 Menthol	18	2.45	99.63	13.61	96.07, 103.32
NRT gum	18	2.46			

Abbreviations: CI = confidence interval; CV = coefficient of variation; LS = least squares; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANOVA model.

Geometrical CV% of the ratio is estimated only for the ratio.

Data Source: [Appendix 15, Table 15.2.4.7](#).

There was no notable difference in COHb levels between THS 2.2 Menthol and NRT gum use both overall and at each post-product use time point, with the 95% CIs spanning 100%.

11.2.3.2 Exhaled CO

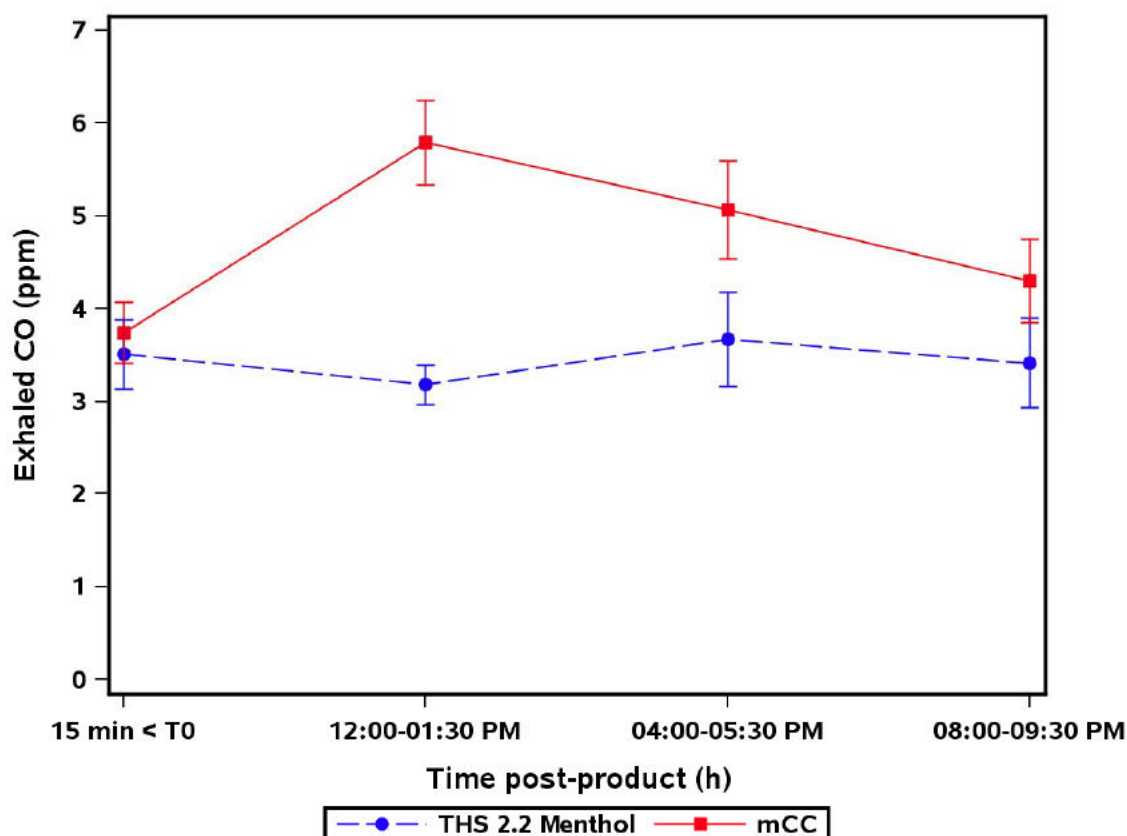
The exhaled levels of CO (ppm) on all study days and the timing of the exhaled CO assessments on single-use and wash-out days are presented by subject in [Appendix 15, Listing 15.3.3.5](#). The exhaled levels of CO following single use are summarized for the Group-1 and Group-2 PK populations in [Appendix 15, Table 15.2.4.10.1](#) and the number of subjects with CO levels ≤ 10 ppm are summarized for each single use measurement in [Appendix 15, Table 15.2.4.10.2](#).

11.2.3.2.1 THS 2.2 Menthol versus mCC

A line graph showing mean exhaled CO levels by product exposure over time following single use for the Group-1 PK population is presented in [Appendix 15, Figure 15.1.2.8.1](#) and in [Figure 11](#).



Figure 11 Mean Exhaled CO (ppm) on Single Use Days (Group-1 PK Population)



Abbreviations: mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.
Data Source: [Appendix 15, Figure 15.1.2.8.1](#).

Mean exhaled CO values following 24 hours of smoking abstinence and prior to product use were 3.5 ppm for THS 2.2 Menthol and 3.7 ppm for mCC, with a comparable range of values for each product prior to use (2 to 9 ppm for THS 2.2 Menthol and 2 to 7 ppm for mCC).

Following single mCC use, mean exhaled CO levels initially increased, reaching a peak of 5.8 ppm at 12:00-01:30 PM; thereafter levels decreased and were close to baseline levels at 08:00-09:30 PM. Following single THS 2.2 Menthol use, mean CO levels remained relatively steady throughout the evaluation period (within the range of 3.2 to 3.7 ppm with the maximum mean level attained at 04:00-05:30 PM).

The results from the statistical analysis of the exhaled CO levels on single use days are presented in [Appendix 15, Table 15.2.4.9](#) and [Table 28](#). A profile of the LS mean



difference (THS 2.2 menthol – mCC) over time is presented for the Group-1 PK population in [Appendix 15, Figure 15.1.2.9.1](#).

Table 28 Analysis of Exhaled CO (Group-1 PK Population)

Product Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 Menthol – mCC)		
			LS Mean	SE	95% CI
THS 2.2 Menthol	43	3.43	-1.62	0.153	-1.92, -1.31
mCC	43	5.05			

Abbreviations: CI = confidence interval; LS = least squares; mCC = menthol conventional cigarette; SE = standard error; THS 2.2 = Tobacco Heating System 2.2.

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: [Appendix 15, Table 15.2.4.9](#).

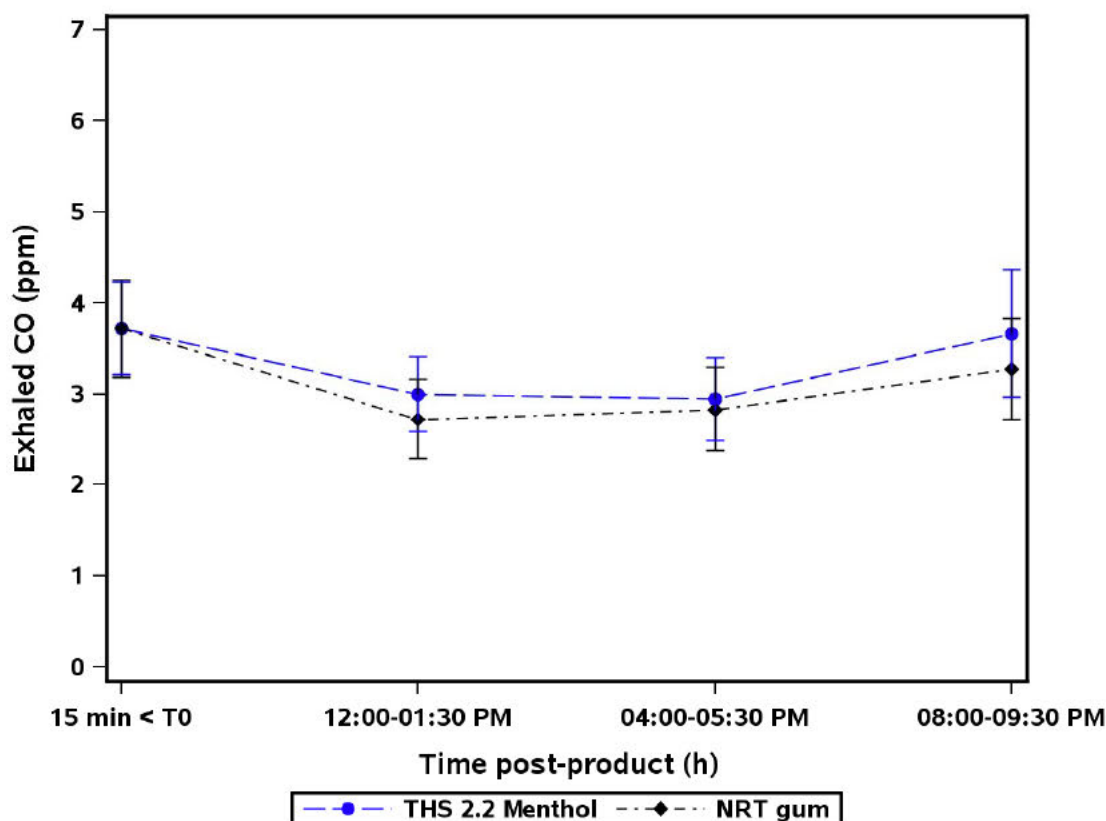
Across the full post-product evaluation period, the LS mean level for exhaled CO following single THS 2.2 Menthol use was 1.62 ppm lower than that determined following single mCC use (95% CI: 1.31, 1.92). Furthermore, the THS 2.2 Menthol - mCC results showed exhaled CO levels to be lower at all individual time points following THS 2.2 Menthol use compared to mCC use at all time points post-product use, with the upper and lower bounds of the 95% CIs below 0.

11.2.3.2.2 THS 2.2 Menthol versus NRT Gum

A line graph showing mean exhaled CO levels by product exposure over time following single use for the Group-2 PK population is presented in [Appendix 15, Figure 15.1.2.8.2](#) and in [Figure 12](#).



Figure 12 Mean Exhaled CO (ppm) on Single Use Days (Group-2 PK Population)



Abbreviations: NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.
Data Source: [Appendix 15, Figure 15.1.2.8.2](#).

Mean exhaled CO values following at least 24 hours of smoking abstinence and prior to product use were 3.7 ppm for both THS 2.2 Menthol and NRT gum with a comparable range of values for each product prior to use (2 to 5 ppm for THS 2.2 Menthol and 2 to 7 ppm for NRT gum). For both products, mean exhaled CO values remained relatively steady throughout the evaluation period (2.9 to 3.7 ppm for THS 2.2 Menthol and 2.7 to 3.3 ppm for NRT gum) with values comparable to baseline observed at 08:00-09:30 PM (3.7 ppm for THS 2.2 Menthol and 3.3 ppm for NRT gum).

The results from the statistical analysis of the exhaled CO levels on single use days are presented in [Appendix 15, Table 15.2.4.9](#) and [Table 29](#). A profile of the LS mean difference (THS 2.2 Menthol - NRT gum) over time is presented for the Group-2 PK population in [Appendix 15, Figure 15.1.2.9.2](#).

**Table 29 Analysis of Exhaled CO (Group-2 PK Population)**

Product Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 Menthol – NRT Gum)		
			LS Mean	SE	95% CI
THS 2.2 Menthol	18	3.20	0.26	0.176	-0.09, 0.61
NRT gum	18	2.94			

Abbreviations: CI = confidence interval; LS = least squares; NRT gum = nicotine replacement therapy gum; SE = standard error; THS 2.2 = Tobacco Heating System 2.2.

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: [Appendix 15, Table 15.2.4.9](#).

Overall there was no notable difference in exhaled CO levels following THS 2.2 Menthol and NRT gum use.

11.3 Statistical and Analytical Issues

11.3.1 Sample Size

Sixty-two smokers were randomized into this study as planned (see [Section 9.7.5](#) for details relating to the determination of the sample size).

11.3.2 Adjustment for Covariates

There was no adjustment for covariates in this study.

11.3.3 Handling of Dropouts or Missing Data

In general, missing data were not imputed in this study, due to the nature of the measurements and the short periods of exposure and use. However, questionnaire data total scores and domain or subscale scores could use a certain degree of imputation (by averaging across individual item scores) as detailed in Section 7.3 of the SAP (see [Appendix 16.1.8](#)). For the analysis of QSU-brief score for NRT gum as compared to THS 2.2 Menthol, the QSU-brief values for NRT gum use at time $T_0 + 15$ minutes were imputed by the QSU-brief values observed at $T_0 + 20$ minutes, given the longer t_{\max} observed for NRT gum use.

No time information was imputed for the computation of the primary PK parameters, therefore, no supportive analysis was conducted.

For PK concentration data:

- LLOQ values before T_0 were considered as zero.
- LLOQ values after C_{last} were not included in the analysis (e.g., for the calculation of AUC).



- Any other LLOQ value (after T_0 and before C_{last}) was queried and, if confirmed, was imputed by $LLOQ/2$.

11.3.4 Interim Analysis and Data Analysis

No interim analysis was planned or conducted for this study.

11.3.5 Multicenter Studies

Not applicable as this was a single-center study.

11.3.6 Multiple Comparison/Multiplicity

No adjustment for multiplicity testing was done as the primary definition of success was the precision of the estimates of the primary endpoint. No claim(s) will be made based on the outcome of the individual tests.

11.3.7 Active Control Studies Intended to Show Equivalence

Not applicable for this study.

11.3.8 Examination of Sub-groups

Results for the exploratory sub-groups are discussed in the appropriate sections along with the main analyses.

11.4 Conclusions

Primary Endpoint

The primary objective for this study was to evaluate the rate and the amount of nicotine absorbed in healthy smokers following single use of THS 2.2 Menthol or mCC. There was no notable difference in the nicotine absorption between THS 2.2 Menthol and mCC as assessed by C_{max} (THS 2.2 Menthol: 10.7 ng/mL; mCC: 12.1 ng/mL) and $AUC_{(0-last)}$ (THS 2.2 Menthol: 24.0 ng.h/mL; mCC: 24.5 ng.h/mL), with THS 2.2 Menthol:mCC geometric LS mean ratios of 88% (95% CI: 69, 114) and 98% (95% CI: 81, 119), respectively. Between-subject variability was high for both C_{max} and $AUC_{(0-last)}$ for both products, with CV% values ranging from 88% to 117% and 83% to 110%, respectively. The within-subject variability was high for both C_{max} (64%) and $AUC_{(0-last)}$ (48%). The within-subject variability reported in this study for C_{max} and $AUC_{(0-last)}$ were greater than the estimates used to calculate the sample size (36% and 21%, respectively). The THS 2.2 Menthol:mCC ratio for $AUC_{(0-last)}$ was estimated with a precision of 21%, while the precision for C_{max} was 26%.



Secondary Endpoints

Secondary Nicotine Pharmacokinetic Parameters - THS 2.2 Menthol versus mCC

There was no notable difference in the amount of nicotine absorbed between THS 2.2 Menthol and mCC as assessed by $AUC_{(0-\infty)}$ (THS 2.2 Menthol: 26.3 ng.h/mL; mCC: 27.7 ng.h/mL; THS 2.2 Menthol:mCC ratio: 95%; 95% CI: 78, 116). The amount of nicotine absorbed as assessed by $AUC_{(0-t)}$ was lower for THS 2.2 Menthol compared to mCC (THS 2.2 Menthol: 0.6 ng.h/mL; mCC: 0.8 ng.h/mL; THS 2.2 Menthol:mCC ratio: 74%; 95% CI: 57, 97). High between-subject variability was noted for both $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ for both products, with CV% values ranging from 85% to 86% and 98% to 160%, respectively. The within-subject variability was high for both $AUC_{(0-\infty)}$ (42%) and $AUC_{(0-t)}$ (67%).

For t_{max} , there was no notable difference between THS 2.2 Menthol and mCC, with a median value of 6 minutes for both products. The $t_{1/2}$ was similar for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 4.1 hours (95% CI: 3.6, 4.7) and 4.0 hours (95% CI: 3.5, 4.6) for mCC, with a THS 2.2 Menthol:mCC ratio of 102% (95% CI: 85, 123).

Nicotine Pharmacokinetic Profiles - THS 2.2 Menthol and mCC

The overall shape of the mean nicotine concentration-time curves was similar for THS 2.2 Menthol and mCC. The plasma concentration versus time profiles following single use of THS 2.2 Menthol and mCC were characterized by a rapid absorption phase with C_{max} reached at the same time post-product use (6 minutes).

Nicotine Pharmacokinetic Parameters - THS 2.2 Menthol versus NRT Gum

Following single use, the maximum exposure to nicotine as assessed by C_{max} was comparable between THS 2.2 Menthol and NRT gum (THS 2.2 Menthol: 7.6 ng/mL; NRT gum: 7.5 ng/mL; THS 2.2 Menthol:NRT gum ratio: 102%; 95% CI: 62, 166; $P = 0.47$). The amount of nicotine absorbed as assessed by $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ were significantly lower for THS 2.2 Menthol compared to NRT gum ($AUC_{(0-last)}$ THS 2.2 Menthol: 15.6 ng.h/mL; NRT gum: 27.9 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 56%; 95% CI: 38, 81. $AUC_{(0-\infty)}$ THS 2.2 Menthol: 15.8 ng.h/mL; NRT gum: 31.1 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 51%; 95% CI: 35, 74. P values were >0.99 for both $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ for the one-sided tests that the exposure was greater for THS 2.2 Menthol compared to NRT gum). The amount of nicotine absorbed as assessed by $AUC_{(0-t)}$ was higher for THS 2.2 Menthol compared to NRT gum but did not achieve statistical significance (THS 2.2 Menthol: 3.4 ng.h/mL; NRT gum: 3.0 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 114%; 95% CI: 79, 163; $P = 0.23$).

High between-subject variability was reported for C_{max} , $AUC_{(0-last)}$, $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$ for both THS 2.2 Menthol and NRT gum, with CV% values ranging from 75%



to 109% for THS 2.2 Menthol and 51% to 75% for NRT gum. The within-subject variability was high for C_{\max} , $AUC_{(0-\text{last})}$, $AUC_{(0-t^*)}$, and $AUC_{(0-\infty)}$ (51% to 79%).

The $t_{1/2}$ was comparable for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 3.2 hours (95% CI: 2.7, 3.8) and 3.5 hours (95% CI: 3.0, 4.1) for NRT gum and a THS 2.2 Menthol:NRT gum ratio of 92% (95% CI: 74, 115).

The t_{\max} was significantly shorter for THS 2.2 Menthol (8 minutes) compared to NRT gum (45 minutes), with a median difference of -38 minutes (95% CI: -45, -32, $P < 0.01$).

Nicotine Pharmacokinetic Profiles - THS 2.2 Menthol and NRT Gum

The overall shape of the mean nicotine concentration-time curves was different for THS 2.2 menthol and NRT gum. The plasma concentration versus time profile following single use was characterized by a rapid absorption phase for THS 2.2 Menthol, while C_{\max} was comparable but attained later following NRT gum use.

Urge-to-smoke Symptoms (QSU-brief)

The average Group-1 PK population urge-to-smoke total score dropped by a maximum of approximately 35% at $T_0 + 15$ minutes and 29% at $T_0 + 30$ minutes following THS 2.2 Menthol and mCC use, respectively, corresponding to maximum reductions of 1.52 and 1.28 point decreases from baseline, respectively. For both THS 2.2 Menthol and mCC, the average total score had not returned to baseline values by the last assessment time point at 12 hours post-product use (90% and 93% of baseline, respectively).

There was no notable difference in QSU-brief total for THS 2.2 Menthol compared to mCC, with an LS mean difference over all time points of -0.3 points for THS 2.2 Menthol - mCC following single use (95% CI: -0.8, 0.2). Consistent results were obtained for the 2 factors, Factor 1 reflecting the desire and intention to smoke with smoking perceived as rewarding (THS 2.2 Menthol - mCC difference of -0.3 (95% CI: -0.9, 0.3); and Factor 2 reflecting anticipation of relief from negative effects of not smoking (THS 2.2 Menthol - mCC difference of -0.2 (95% CI: -0.8, 0.3). The difference between THS 2.2 Menthol and mCC for the total score was greatest at $T_0 + 15$ minutes with a THS 2.2 Menthol - mCC difference of -0.4 (95% CI -1.1, 0.3).

In the Group-2 PK population, the average urge-to-smoke total score dropped by approximately 28% and 22% following THS 2.2 Menthol and NRT gum use, respectively. For THS 2.2 Menthol, the maximum decrease was observed at $T_0 + 30$ minutes and at $T_0 + 45$ minutes for NRT gum, with maximum reductions corresponding to a 1.1 and 0.9 point decrease from baseline, respectively. The average total scores for both products were below their respective baseline values at 12 hours post-product use (95% and 90% for THS 2.2 Menthol and NRT gum, respectively).



There was no notable difference in QSU-brief total score for THS 2.2 Menthol compared to NRT gum, with an LS mean difference over all time points of -0.3 points for THS 2.2 Menthol – NRT gum following single use (95% CI: -0.9, 0.2). Consistent results were obtained for the 2 factors, Factor 1 THS 2.2 Menthol - NRT gum difference of -0.3 (95% CI: -1.0, 0.4), and Factor 2 THS 2.2 Menthol - NRT gum difference of -0.4 (95% CI: -0.7, -0.1). The difference between THS 2.2 Menthol and NRT gum for the total score was greatest at $T_0 + 15$ and 20 minutes, where the applicable assessment time points apply for the products, with a THS 2.2 Menthol - NRT gum difference of -0.8 (95% CI -1.7, 0.1).

Product evaluation questionnaire (MCEQ)

Based on the results from the product comparison using the MCEQ subscale scores following single use, differences were observed for two subscales, with enjoyment of respiratory tract sensation being 0.6 points (95% CI: 0.1, 1.1) lower and smoking satisfaction being 1.1 points (95% CI: 0.7, 1.5) lower for THS 2.2 Menthol compared to mCC.

There was no notable difference in aversion, craving reduction, and psychological reward between THS 2.2 Menthol and mCC following single use, with aversion being 0.1 points (95% CI: -0.4, 0.6) lower, craving reduction being 0.1 points (95% CI: -0.3, 0.5) lower, and psychological reward being 0.2 points lower (95% CI: 0.0, 0.4) for THS 2.2 Menthol than mCC.

Blood COHb

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.5% for both THS 2.2 Menthol and mCC. Fifteen minutes after product use, the mean value had increased to 3.5% for mCC, while COHb remained stable for the 12 hour post-product evaluation period for THS 2.2 Menthol users (within the range of 2.4% to 2.6%, with the maximum achieved at $T_0 + 60$ minutes). Across the full 12 hour post-product evaluation period, the THS 2.2 Menthol:mCC ratio for COHb was 81% (95% CI: 79, 84) after single use.

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.4% for both THS 2.2 Menthol and NRT gum. Following THS 2.2 Menthol and NRT gum use, there was no notable difference in overall mean COHb levels between THS 2.2 Menthol and NRT gum users. Mean COHb levels remained relatively unchanged throughout the assessment day (2.4% to 2.5% for THS 2.2 Menthol and 2.4% to 2.5% for NRT gum), with the maximum COHb value achieved at $T_0 + 4$ hours for both products.



Exhaled CO

Mean exhaled CO values following 24 hours of smoking abstinence and prior to product use were 3.5 ppm for THS 2.2 Menthol and 3.7 ppm for mCC. Following single mCC use, the mean exhaled CO levels initially increased, reaching a peak of 5.8 ppm at 12:00-01:30 pm (the first post-product use assessment). Following single THS 2.2 Menthol use, mean CO levels remained relatively steady throughout the evaluation period (within the range of 3.2 to 3.7 ppm with the maximum mean level attained at 04:00-05:30 PM). Across the full post-product evaluation period, the LS mean level for exhaled CO following single THS 2.2 Menthol use was 1.6 ppm lower than that determined following single mCC use (95% CI: 1.3, 1.9).

Mean exhaled CO values following at least 24 hours of smoking abstinence and prior to product use were 3.7 ppm for both THS 2.2 Menthol and NRT gum. Following THS 2.2 Menthol and NRT gum use, there was no notable difference in overall exhaled CO levels. For both products, mean exhaled CO values remained relatively steady throughout the evaluation period (2.9 to 3.7 ppm for THS 2.2 Menthol and 2.7 to 3.3 ppm for NRT gum) with values comparable to baseline observed at 08:00-09:30 PM (3.7 ppm for THS 2.2 Menthol and 3.3 ppm for NRT gum).

Summary

Primary Objective

- There was no notable difference in uptake and the amount of nicotine absorbed following THS 2.2 Menthol and mCC use as assessed by C_{\max} and $AUC_{(0-\text{last})}$, with the 95% CIs for both parameters spanning 100%. The THS 2.2 Menthol:mCC ratio for $AUC_{(0-\text{last})}$ was estimated with a precision of 21%, while the precision for C_{\max} was 26%.

Secondary Objectives

- Following THS 2.2 Menthol and NRT gum use, maximum exposure to nicotine as assessed by C_{\max} was comparable, while the amount of nicotine absorbed as assessed by $AUC_{(0-\text{last})}$ was significantly lower following THS 2.2 Menthol use compared to NRT gum.
- The amount of nicotine absorbed as assessed by $AUC_{(0-\infty)}$ was comparable, while $AUC_{(0-t)}$ was lower following THS 2.2 Menthol use compared to mCC. The amount of nicotine absorbed as assessed by $AUC_{(0-\infty)}$ was significantly lower, while $AUC_{(0-t)}$ was higher but not statistically significantly so following THS 2.2 Menthol use compared to NRT gum.
- Following THS 2.2 Menthol and mCC use, median t_{\max} was observed at 6 minutes for both products. Following THS 2.2 Menthol and NRT gum use, the median t_{\max} was significantly shorter for THS 2.2 Menthol compared to NRT gum.



-
- THS 2.2 Menthol use decreased the urge-to-smoke more than mCC use, although there was no notable difference considering the mean over all time points. THS 2.2 Menthol use also decreased the urge-to-smoke more than NRT gum use, particularly for the first 4 hours post-product use, although there was no notable difference considering the mean over all time points.
 - The assessment of subjective product evaluation suggested that mCC use was more satisfying and provided a more enjoyable respiratory tract sensation compared to THS 2.2 Menthol. There was no notable difference in craving reduction, psychological reward, or aversion following THS 2.2 Menthol use compared to mCC.
 - There was no increase in either blood COHb or exhaled CO levels following THS 2.2 Menthol or NRT gum use, however blood COHb and exhaled CO levels increased following mCC use, resulting in higher levels of COHb and CO compared to THS 2.2 Menthol and NRT gum use.



12 SAFETY EVALUATIONS

The safety endpoints were analyzed using the safety population. The safety population consisted of 73 subjects: 62 randomized subjects (22 subjects in the THS 2.2 Menthol – mCC sequence, 22 subjects in the mCC – THS 2.2 Menthol sequence, 9 subjects in the THS 2.2 Menthol – NRT gum sequence, and 9 subjects in the NRT gum – THS 2.2 Menthol sequence) and 11 non-randomized subjects who were exposed to THS 2.2 Menthol and NRT gum from the product trials on Day -1. Unless otherwise stated, 73 was the denominator used for the calculation of percentages following THS 2.2 Menthol exposure, including all events that occurred from after the product test of THS 2.2 Menthol or NRT gum at Admission.

12.1 Adverse Events

12.1.1 Brief Summary of Adverse Events

Adverse events are listed by subject in [Appendix 15, Listing 15.3.6.1.1](#).

An overall summary of AEs is presented for the safety population by sequence in [Appendix 15, Table 15.2.6.1](#) and [Table 30](#).


Table 30 Summary of Adverse Events (Safety Population)

	Sequence					Overall Safety (N=73)
	THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NRT gum (N=9)	NRT gum - THS 2.2 Menthol (N=9)	Exposed not randomized (N=11)	
Number of:						
AEs	1	2	0	1	0	4
SAEs	0	0	0	0	0	0
Severe AEs	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0
AEs related to IP	0	0	0	0	0	0
AEs related to study procedures	0	0	0	0	0	0
Number (%) of subjects with						
AEs	1 (4.5%)	2 (9.1%)	0	1 (11.1%)	0	4 (5.5%)
AEs related to IP	0	0	0	0	0	0
AEs related to NRT gum	0	0	0	0	0	0
AEs related to study procedures	0	0	0	0	0	0

Abbreviations: AE = adverse event; IP = investigational product; mCC = menthol conventional cigarette; N = number of subjects randomized; NRT gum = nicotine replacement therapy gum; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2.

Percentages were calculated using the N of subjects in the column headers.

Data Source: [Appendix 15, Table 15.2.6.1.](#)

There were no SAEs or severe AEs reported during the study and no subjects discontinued from the study due to an AE. Overall, there were only 4 AEs reported in 4 of the 73 subjects (5.5%) in the safety population, and all were mild in severity.

The incidence of AEs was very low. Only 1/22 subjects (4.5%) in the THS 2.2 Menthol – mCC sequence, 2/22 subjects (9.1%) in the mCC – THS 2.2 Menthol sequence, and 1/9 subjects (11.1%) in the NRT gum – THS 2.2 Menthol sequence reported AEs. None of the subjects in the THS 2.2 Menthol – NRT gum sequence or the subjects who were exposed but not randomized reported an AE.

No AEs were assessed as being related to IP (THS 2.2 Menthol or mCC), NRT gum, or study procedures.



12.1.2 Display of Adverse Events

Adverse events are summarized by sequence for the safety population by SOC and PT in [Appendix 15, Table 15.2.6.2.1](#) and [Table 31](#), by SOC in [Appendix 15, Table 15.2.6.2.2](#), and by PT in [Appendix 15, Table 15.2.6.2.3](#).

Table 31 Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred term	Sequence					Overall Safety (N=73)
	THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NRT gum (N=9)	NRT gum - THS 2.2 Menthol (N=9)	Exposed not randomized (N=11)	
Number (%) subjects with any AEs	1 (4.5%)	2 (9.1%)	0	1 (11.1%)	0	4 (5.5%)
Investigations						
Bilirubin conjugated increased	0	1 (4.5%)	0	0	0	1 (1.4%)
Blood bilirubin increased	0	1 (4.5%)	0	0	0	1 (1.4%)
Hemoglobin decreased	0	0	0	1 (11.1%)	0	1 (1.4%)
Lymphocyte count increased	1 (4.5%)	0	0	0	0	1 (1.4%)

Abbreviations: AE = adverse event; mCC = menthol conventional cigarette; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.

Terms coded using MedDRA® version 16.0.

Percentages were calculated using the N of subjects in the column headers.

Data Source: [Appendix 15, Table 15.2.6.2.1](#).

The SOC for all reported AEs was investigations. Subject 0027 (THS 2.2 Menthol – mCC) reported lymphocyte count increased, Subject 0010 (mCC – THS 2.2 Menthol) reported bilirubin conjugated increased, Subject 0093 (mCC – THS 2.2 Menthol) reported blood bilirubin increased, and Subject 0083 (NRT gum – THS 2.2 Menthol) reported hemoglobin decreased.

12.1.3 Analysis of Adverse Events

12.1.3.1 Analysis of Adverse Events by Severity

Adverse events are summarized by severity (mild, moderate, or severe), SOC, and PT for the safety population by sequence in [Appendix 15, Table 15.2.6.5](#).

All AEs were mild in severity.



12.1.3.2 Analysis of Adverse Events by Relationship

12.1.3.2.1 Adverse Events Related to Investigational Product or Reference Point Product

Adverse events related to IP (THS 2.2 Menthol or mCC) or reference point product (NRT gum) are summarized by SOC and PT for the safety population by sequence in [Appendix 15, Table 15.2.6.3](#).

No AEs were assessed as being related to the use of IP or NRT gum.

12.1.3.2.2 Adverse Events Related to Study Procedures

Adverse events related to study procedures are summarized by SOC and PT for the safety population by sequence in [Appendix 15, Table 15.2.6.6](#).

No AEs were assessed as being related to study procedures.

12.1.4 Listing of Adverse Events by Subject

Adverse events are listed by subject in [Appendix 15, Listing 15.3.6.1.1](#).

12.1.5 Investigational Device Malfunction or Misuse Events

Device events and malfunctions including an assessment of whether the event was related to an AE are listed by subject in [Appendix 15, Listing 15.3.6.2](#). Device events and malfunctions are summarized by sequence for the safety population in [Appendix 15, Table 15.2.6.7](#).

None of the subjects experienced a device event or malfunction.

12.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.2.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Serious AEs and AEs that led to withdrawal from the study are listed by subject in [Appendix 15, Listing 15.3.6.1.2](#) and [Appendix 15, Listing 15.3.6.1.3](#), respectively.

None of the subjects was withdrawn from the study due to an SAE or AE.

12.2.1.1 Deaths

No deaths occurred in this study.



12.2.1.2 Other Serious Adverse Events

No SAEs occurred during the study for any randomized subject.

12.2.1.3 Other Significant Adverse Events

No withdrawals due to AEs occurred in this study.

12.2.2 Narratives of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths, SAEs, or other significant AEs occurred in this study.

12.2.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths, SAEs, or other significant AEs occurred in this study.

12.3 Clinical Laboratory Evaluation

12.3.1 Clinical Chemistry

Clinical chemistry data are presented by subject in [Appendix 15, Listing 15.3.6.4](#) including individual changes and shifts from Admission to Discharge and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Clinical chemistry data are summarized for the safety population in [Appendix 15, Table 15.2.6.10](#) including summaries of low, normal, high, and abnormal clinically relevant results.

One clinically relevant result was observed for clinical chemistry values at Screening, Admission, or Day of Discharge for 1 subject in the mCC – THS 2.2 Menthol sequence with a high bilirubin value at Admission. The majority of subjects in all sequences had normal clinical chemistry values at Screening, Admission, and Day of Discharge. In general, mean changes from baseline in clinical chemistry were small and comparable between sequences.

For most parameters, only a small number of subjects deviated (high or low) from normal at Day of Discharge. The clinical chemistry parameters for which ≥ 2 subjects in each sequence had a shift from normal to low included LDH, blood urea nitrogen, protein, and creatinine. None of these changes were clinically significant.

The clinical chemistry parameters for which ≥ 2 subjects had a shift from normal to high were triglycerides and bilirubin. None of these changes were clinically significant.



The majority of clinical chemistry variables were normal or classified as grade 1 (mild) on the toxicity grading. No subjects reported clinical chemistry variables classified as grade 2 (moderate) or higher on the toxicity grading after the product test at Admission including/until the Day of Discharge.

12.3.2 Hematology

Hematology data are presented by subject in [Appendix 15, Listing 15.3.6.5](#) including individual changes and shifts from Admission to Discharge and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Hematology data are summarized for the safety population in [Appendix 15, Table 15.2.6.11](#) including summaries of low, normal, high, and abnormal clinically relevant results.

No results of clinical relevance were observed for hematology values at Screening, Admission, or Day of Discharge. The majority of subjects in all sequences had normal hematology values at Screening, Admission, and Day of Discharge. In general, mean changes from baseline in hematology parameters were small and comparable between sequences.

For most parameters, only a small number of subjects in each sequence deviated (high or low) from normal at Day of Discharge. The hematology parameters for which ≥ 2 subjects in each sequence had a shift from normal to low included hematocrit, and erythrocytes. None of these changes were clinically significant.

The hematology parameters for which ≥ 2 subjects in each sequence had a shift from normal to high included monocytes/leukocytes, mean corpuscular hemoglobin concentration, and eosinophils/leukocytes. None of these changes were clinically significant.

The majority of hematology results were normal or classified as grade 1 (mild) on the toxicity grading. No subjects reported hematology results which were classified as grade 2 (moderate) or higher on the toxicity grading after the product test at Admission including/until the Day of Discharge.

12.3.3 Urinalysis

Urinalysis data are presented by subject in [Appendix 15, Listing 15.3.6.6](#) including individual changes and shifts from Admission to Discharge and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Urinalysis data are summarized for the safety population in [Appendix 15, Table 15.2.6.12](#) including summaries of low, normal, high, and abnormal clinically relevant results.



The majority of subjects in all sequences had normal urinalysis results at Screening, Admission, and Day of Discharge. In general, urinalysis results were comparable between sequences and any mean changes from baseline in pH and specific gravity were small and comparable between sequences. A number of clinically relevant urinalysis results were observed at Screening, Admission, and Day of Discharge, however the majority of these were positive occult blood results in female subjects.

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

12.4.1 Vital Signs

Vital signs data are presented by subject in [Appendix 15, Listing 15.3.6.7](#) including individual changes from baseline.

Vital signs data are summarized for the safety population in [Appendix 15, Table 15.2.6.13](#) including summaries of changes from baseline at each assessment time point.

The mean and median data for all vital signs parameters analyzed were unremarkable and comparable between sequences. In general, mean changes from baseline in vital signs parameters were small and comparable between sequences. No clinically relevant abnormalities were observed for any subject.

12.4.2 Physical Examinations

Physical examination findings (including height, weight, and BMI) are presented by subject in [Appendix 15, Listing 15.3.6.10](#).

Abnormal physical examination findings at Admission, and Discharge, and their clinical relevance, are summarized for the safety population in [Appendix 15, Table 15.2.6.17](#). Weight and BMI data are summarized for the safety population in [Appendix 15, Table 15.2.6.16](#).

In all sequences, no abnormal or clinically relevant physical examination findings were recorded at Screening, Admission, or Day of Discharge.

Mean body weight and BMI were comparable between sequences and changes from baseline were small and comparable between sequences.



12.4.3 ECG

The ECG data are presented by subject in [Appendix 15, Listing 15.3.6.9](#) including individual changes from baseline, shifts from baseline in overall ECG interpretation, and a description of clinical relevance.

The ECG data are summarized for the safety population in [Appendix 15, Table 15.2.6.14](#) including summaries of changes from baseline at each assessment time point.

No clinically relevant differences in ECG parameters or in changes from baseline were observed between sequences.

No subject reported an abnormal, clinically significant ECG finding, or findings that had shifted from normal to abnormal compared with baseline.

12.4.4 Spirometry

Spirometry data are presented by subject in [Appendix 15, Listing 15.3.6.8](#).

Spirometry results for the safety population are summarized in [Appendix 15, Table 15.2.6.15](#) including summaries of changes from Admission to Discharge.

In all sequences, all subjects had post-bronchodilator $FEV_1/FVC > 0.7$, post-bronchodilator $FEV_1 > 80\%$ of predicted, and post-bronchodilator $FVC > 80\%$ of predicted at Screening.

For all sequences, no notable changes from baseline in spirometry parameters were observed at either Admission or Day of Discharge and all results were interpreted as normal.

12.4.5 Assessment of Cough

Subject listings for the assessment of cough are presented by subject in [Appendix 15, Listing 15.3.6.13](#).

The results for the assessment of cough intensity during the study using Likert scales are summarized for the safety population in [Appendix 15, Table 15.2.6.18](#). The results for the assessment of cough impact (how bothersome the cough was using a VAS), cough intensity, frequency, and amount of sputum production, by study day are summarized for the safety population by study day in [Appendix 15, Table 15.2.6.18.1](#). The assessments performed at Day 0 to Day 4 were used to evaluate cough at Day -1 to Day 3.

Overall, there were no increases in frequency or intensity of cough following THS 2.2 use. The number of subjects who experienced a cough during the study period was higher in the THS 2.2 Menthol – mCC sequence (14 subjects [63.6%]) and the THS 2.2 Menthol



– NRT gum sequence (7 subjects [77.8%]) than in the mCC – THS 2.2 Menthol sequence (9 subjects [40.9%]) or the NRT gum – THS 2.2 Menthol sequence (5 subjects [55.6%]). Moderate intensity coughs were experienced by 1 subject in all 4 sequences, however none of these occurred following THS 2.2 use. One subject in the THS 2.2 Menthol – mCC sequence experienced a severe intensity cough on Day 0. During the course of the study, the mean VAS score either decreased between Admission and Discharge or was low throughout (THS 2.2 Menthol – NRT gum). All subjects who had experienced a regular need to cough assessed their cough frequency as either rarely (Likert score of 1) or sometimes (Likert score of 2), with the exception of 2 subjects in the THS 2.2 Menthol – mCC sequence who experienced a fairly often need to cough (Likert score of 3) on Day -1 and Day 0. All of the subjects assessed their sputum production as either no sputum (Likert score of 0) or as a moderate amount of sputum (Likert score of 1).

12.5 Safety Conclusions

There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE.

Overall, there were only 4 AEs (lymphocyte count increased, bilirubin conjugated increased, blood bilirubin increased, and hemoglobin decreased) reported by 4 of the 73 subjects (5.5%) in the safety population (which included 11 subjects who were enrolled but not randomized). All 4 AEs were mild in severity. None of the subjects who were exposed but not randomized reported an AE. No AEs were assessed as being related to IP (THS 2.2 Menthol or mCC), NRT gum, or study procedures.

None of the subjects experienced a device event or malfunction.



13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The purpose of this study was to compare the profile of nicotine uptake (rate and amount of nicotine absorbed), the subjective effects, and the safety profile in smoking Japanese healthy subjects switching from mCC to THS 2.2 Menthol. As a reference point, a similar comparison was made in subjects switching from mCC to THS 2.2 Menthol or the NRT gum.

Pharmacokinetic comparisons:

The mean nicotine PK profiles following THS 2.2 Menthol and mCC use were similar, with the concentration-time curves for both products almost superimposed upon one another.

The amount of nicotine absorption, as assessed by $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$ was comparable following a single use of THS 2.2 Menthol and mCC. The rate of nicotine absorption, as assessed by C_{max} and t_{max} , was also comparable between the 2 products, with mCC parameters similar to published data for a Japanese population [34]. This is indicative of a pulmonary absorption of nicotine with THS 2.2 Menthol, similarly to mCC as expected.

In terms of precision and variability, the within-subject variability observed for C_{max} (64%) and $AUC_{(0-last)}$ (48%) in this study were greater than the estimates used to calculate the sample size (36% and 21%, respectively). As a consequence, the precision of THS 2.2 Menthol:mCC ratio estimate for C_{max} (26%) and $AUC_{(0-last)}$ (21%) were slightly exceeding the $\pm 20\%$ target. For future studies, a larger margin of error (up to $\pm 30\%$) could be considered appropriate for the evaluation criteria in nicotine PK assessment studies, as suggested by the bioequivalence guidelines for highly variable drugs [25] and accounting for both the variability in product use and the short adaptation period.

Exploratory sub-group analyses were conducted on C_{max} and $AUC_{(0-last)}$ for gender and ISO nicotine levels sub-groups. Results were in general consistent with those from the primary analysis, however, C_{max} was lower for THS 2.2 Menthol compared to mCC for female subjects but comparable in male subjects. The number of subjects was small, and future studies should indicate if any gender differences exist. Differences were observed in both the low (≤ 0.6 mg ISO) and high nicotine level smokers (> 0.6 to ≤ 1 mg ISO), with PK parameters higher for low nicotine level smokers, and lower for high nicotine level smokers for THS 2.2 Menthol compared to mCC. These results are consistent with the nicotine content of THS 2.2 Menthol (0.5 mg ISO), which is approximately between the 2 ISO nicotine levels sub-groups. With a longer adaptation period, it might be expected that this difference would attenuate over time, since the smokers tend to self-titrate



The $t_{1/2}$ values were comparable between THS 2.2 Menthol and mCC at approximately 4 hours [34], with values exceeding 8 hours in several subjects. This value is longer than what has been previously reported in the literature for a Caucasian population (2 to 2.5 hours [35]). The wash-out durations of 33 to 38 hours prior to Day 1 single product use and 47 to 49 hours prior to Day 3 single product use in this study, were probably not sufficient to completely eliminate the nicotine. This could be one of the reason why plasma nicotine concentrations were still quantifiable (>0.2 ng/mL) for a number of subjects prior to product use on Day 1 (31 subjects) and of these subjects, some were also quantifiable on Day 3 (10 subjects). The Japanese population exhibits a higher frequency of cytochrome P450 CYP2A6 polymorphism, an enzyme responsible primarily for the metabolism of nicotine, as compared to the Caucasian population [36, 37]. The high prevalence of slow metabolizers in the Japanese population could partially explain the longer than expected $t_{1/2}$, as previously observed in smokers with an average CYP2A6 activity of 50% [38].

The nicotine PK profiles following THS 2.2 and NRT gum use were different, with a faster rate of nicotine absorption observed for THS 2.2 Menthol compared to NRT gum, as expected. The amount of nicotine absorbed (as assessed by $AUC_{(0-last)}$ and $AUC_{(0-\infty)}$) was significantly lower following THS 2.2 Menthol use compared to NRT gum, which was unexpected. However, the amount of nicotine absorbed following THS 2.2 Menthol use in the Group-2 PK population was approximately 35% to 40% lower than that of the Group-1 PK population following THS 2.2 Menthol use. The reason for this difference between the 2 groups is unknown. Mean $t_{1/2}$ values were similar between THS 2.2 Menthol and NRT gum and consistent with the values from the comparison THS 2.2 Menthol and mCC (see discussion above). The nicotine content in the NRT gum (2 mg) used in this study is different from THS 2.2 Menthol (0.5 mg ISO), but the route of absorption is also different. Using NRT gum, the nicotine is released progressively over time by chewing the gum. The PK profile (and amount of nicotine absorbed) is dependent on the chewing time, chewing pressure, salivation [39] and follows an oral administration route. In contrast, the nicotine generated by the THS 2.2 Menthol aerosol is inhaled and absorbed mainly in the lung over a shorter period of time.

Subjective effects:

Given the similarity in nicotine PK profiles following THS 2.2 Menthol and mCC use, the reduction in urge-to-smoke, as assessed by the total score of the QSU-brief questionnaire, was expected to be similar between the 2 products. In the study, THS 2.2 Menthol and mCC had a similar overall shape for the urge-to-smoke profile over time, with a larger maximum reduction from baseline following THS 2.2 Menthol use compared to mCC observed at 15 minutes post-product use for both products. The results for the total and factor scores were consistent with the comparison of the figures in showing a greater decrease in urge-to-smoke following THS 2.2 Menthol use compared to mCC, however, considering the effect over all time points, there was no notable difference in



urge-to-smoke between THS 2.2 Menthol and mCC, with the 95% CIs for total score, Factor 1, and Factor 2 spanning zero. The craving reduction subscale derived from the MCEQ, also indicated no notable difference between the products.

From the MCEQ questionnaire, mCC use was more satisfying and provided a more enjoyable respiratory tract sensation compared to THS 2.2 Menthol use, while there was no notable difference between the 2 products for aversion and psychological reward. These differences can be partly explained by the fact that subjects are new to THS 2.2 Menthol, being more familiar with and usually attached to mCC. In fact, the use of THS 2.2 Menthol is a new experience for the smokers, with a product offering a different ritual (need of an electric device, look, and feel) and flavour profile (due to a different tobacco blend composition and tobacco heated at a different temperature) that requires some adaptations for the smoker.

Given the shorter t_{\max} following THS 2.2 Menthol use compared to NRT gum use, the reduction in urge-to-smoke was expected to be faster for THS 2.2 Menthol than NRT gum. The maximum decrease from baseline in total score in urge-to-smoke was more pronounced and faster for THS 2.2 Menthol (15 to 30 minutes) than for NRT gum (45 minutes). The mean QSU-brief total score over all time points was lower for THS 2.2 Menthol compared to NRT gum. Since smokers are used to having a fast relief of the urge-to-smoke symptoms associated with nicotine withdrawal, the higher and faster QSU-brief total score reduction observed with THS 2.2 Menthol compared to NRT gum would suggest that THS 2.2 Menthol is a better alternative to NRT gum, in terms of urge-to-smoke reduction.

Biomarkers and safety:

Following single use, the exposure to CO (as assessed by blood COHb and exhaled CO levels) remains at levels found during the wash-out following THS 2.2 Menthol and NRT gum use, while exposure to CO increased following mCC use, as expected. As a consequence, mean COHb and exhaled CO levels were lower at all individual time points following THS 2.2 Menthol use compared to mCC. There were no notable differences in the levels of mean COHb or exhaled CO following THS 2.2 Menthol use compared to NRT gum following single use.

There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE. Overall, the incidence of AEs was very low, with only 4 AEs reported by 4 subjects in the safety population. All AEs were mild in severity and no subjects experienced an AE that was considered as related to either THS 2.2 Menthol or mCC use. Based on the known safety profile of mCC or NRT, no AEs of concern occurred.

There were no clinically relevant trends in safety laboratory parameters, vital signs, physical examination, ECG, spirometry findings, or assessment of cough.

**Study Limitations:**

In this study, relatively high between-subject variability for C_{\max} was observed in the Group-1 PK population, particularly following THS 2.2 menthol use (117%). The variability was likely driven by values which were either a third of, or 3 times larger, than the mean. Six PK profiles from 5 subjects had C_{\max} values below 3 ng/mL, and 5 profiles from 3 subjects had C_{\max} values above 34 ng/mL following use of either THS 2.2 Menthol or mCC, compared with a mean value of approximately 11 to 12 ng/mL for both products. Whereas lower than expected C_{\max} values could be explained by limited drawing, or inhalation of the aerosol by the subjects, higher C_{\max} values are harder to explain. These results might be linked to individual variations in the smoking pattern of smokers (e.g., volume and number of puffs, interval between puffs), which were not assessed in this study. One subject (Subject 0135) displayed unexpectedly high C_{\max} values of 58 and 44 ng/mL at Day 1 and Day 3 following mCC and THS 2.2 Menthol use, respectively. No protocol deviation or bioanalytical issue besides a relatively low CYP2A6 activity (7.75%) could explain these results. The subject's nicotine concentrations before product use were quantifiable, but low, at 0.8 ng/mL and 0.2 ng/mL at Day 1 and Day 3, respectively, but the PK profiles appeared normal considering the high C_{\max} values, with t_{\max} occurring at 6 minutes.

Despite normal PK profiles, 2 additional subjects presented 4 profiles with notably high C_{\max} values of approximately 32 to 38 ng/mL, following use of both products. Only 1 PK profile had a $t_{1/2}$ which could not be calculated.

The Group-1 PK t_{\max} results showed 8 subjects with values ≥ 30 minutes. With the exception of 1 subject, low CYP2A6 activity values at Day -1 were reported by these subjects, ranging from approximately 8% to 16%, which indicates slow nicotine metabolism [40]. A t_{\max} value of 720 minutes was recorded for 2 subjects 12 hours post-THS 2.2 Menthol use. The second peak associated with these PK profiles were higher than the first peak observed 15 minutes post-product use. No reasonable explanation could be found.

The longer than expected $t_{1/2}$ might be associated with the sampling and analytical design. The sampling period was longer in this study (over a 24 hour period) as compared to most of the nicotine PK studies published in the literature. Moreover, the last samples were taken during night-time, when the renal clearance is reduced as a function of the hepatic blood flow decline [10, 41]. Additionally, the analytical method used in this study was very sensitive (LLOQ of 0.2 ng/mL), whereas the LLOQ values typically reported in the literature are approximately 0.5 to 1 ng/mL [34, 42, 43]. This could have led to an underestimation of $t_{1/2}$. In another publication [41], a $t_{1/2}$ of 11 hours was calculated using the time course of urinary excretion of nicotine. This method was reported to be more sensitive in detecting lower levels than plasma levels. It is unclear if the longer than expected $t_{1/2}$ is the result of race (high CYP2A6 polymorphism in Japanese associated



with higher incidence of slow metabolizers), low LLOQ, long period of sampling collection, or a combination of all of these parameters. In addition, 3 subjects with long $t_{1/2}$ values of 12.0, 11.5, and 11.6 hours were all flagged as the estimations were calculated over a period of less than 2 half-lives, which is a potential hindrance to a correct estimation.

Additional studies combining higher LLOQ and sampling collection times could provide further insights on the relation of a prolonged $t_{1/2}$ and analytical designs.

A carry-over effect between study sequences was observed due to the prolonged and unexpected $t_{1/2}$, however the impact was considered to have a negligible influence in this study. This was shown by the results of the sensitivity analysis conducted according to the recommendations of European Medicines Agency guideline on the investigation of bioequivalence [26], excluding subjects with T_0 values higher than 5% of the C_{max} . As an improvement to the design of any subsequent studies, a longer wash-out period could be used prior to the first product use to ensure a uniform wash-out period prior to each product use and to reduce the carry-over.

To better define the satisfaction and acceptance of the product, studies of longer duration (consumer or clinical studies) or with a longer run-in period, to test and get used to THS 2.2 Menthol, would be required.

Other studies with multiple use, and *ad libitum* use, which are part of our clinical program to assess THS 2.2 Menthol, will provide further information on satisfaction, adaptation to the product, additional safety information, and reduced risk-diseases.

13.2 Overall Conclusions

In this study, the amount of nicotine absorbed was comparable following THS 2.2 Menthol single use when compared to mCC single use. Nicotine was absorbed and eliminated at a similar rate for the 2 products. The results for mCC were consistent with what has previously been reported in the literature. THS 2.2 Menthol single use decreased the urge-to-smoke in a comparable fashion to mCC single use at any time point post-product use. Results from other subjective effects of smoking suggested that THS 2.2 Menthol use was less satisfying and provided a less enjoyable respiratory tract sensation compared to mCC. No notable difference was observed between the 2 products in aversion and psychological reward.

This study demonstrated that nicotine was absorbed more rapidly following THS 2.2 Menthol compared to NRT gum. However, it was also observed that the amount of nicotine absorbed was significantly lower following THS 2.2 Menthol compared to NRT gum, while the elimination rate was comparable for the 2 products. THS 2.2 Menthol use reduced craving faster than NRT gum, but the overall time profile showed no notable difference in urge-to-smoke between THS 2.2 Menthol and NRT gum use. However,



THS 2.2 Menthol use decreased the urge-to-smoke more than NRT gum use for the first 4 hours post-product use.

In contrast to mCC single use, where CO exposure increased rapidly, no increase in CO exposure was observed following THS 2.2 Menthol or NRT gum single use.

No SAEs or severe AEs were reported during this study, with no AEs related to IP use.



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15 ADDITIONAL SUMMARIES NOT INCLUDED IN THE TEXT

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15.1.2 Secondary Endpoints

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15.1.3 Other Assessments

Not applicable.

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15.3.3 Listing of Pharmacokinetic and Biomarker Data

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15.3.4 Other Assessments

Not applicable.

15.3.5 Human Smoking Topography Assessment

Not applicable.

15.3.6 Safety, Questionnaire, and Comments Data Listings

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15.4 Statistical Output

15.4.1 Disposition and Background Data

Not applicable.

15.4.2 Product Use

Not applicable.

15.4.3 Primary Endpoints

[Listing 15.4.3.1](#) Analysis of Primary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population

[Listing 15.4.3.2](#) Analysis of Primary Pharmacokinetic Parameters of Nicotine by Sex and Nicotine Level – Group-1 PK Population

15.4.4 Secondary Endpoints

[Listing 15.4.4.1](#) Analysis of Secondary Pharmacokinetic Parameters of Nicotine – Group-1 PK Population

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[Listing 15.4.4.3.1](#) Analysis of Pharmacokinetic Parameters of Nicotine by Bootstrapping Techniques – PK Population

[Listing 15.4.4.3.2](#) Supportive Analysis of Pharmacokinetic Parameters of Nicotine Excluding Subject with T_0 Value >5% of Their C_{\max} Value - PK Population

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[Listing 15.4.4.15](#) Analysis of MCEQ Subscales – PK Population

[Listing 15.4.4.16](#) Analysis of MCEQ Subscales by Bootstrapping Techniques – PK Population



16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

- 16.1.1.1 Study Protocol (English Version)
- 16.1.1.2 Study Protocol (Local Language Version)
- 16.1.1.3 Protocol Amendments
- 16.1.1.4 Notes to File

16.1.2 Sample Case Report Form, Subject Questionnaire, and Subject Smoking Diary

- 16.1.2.1 Sample Case Report Form
- 16.1.2.2 Subject Questionnaire English
- 16.1.2.3 Subject Questionnaire Local Language
- 16.1.2.4 Subject Smoking Diary English
- 16.1.2.5 Subject Smoking Diary Local Language

16.1.3 List of IRBs, IRB Approvals, Sample Consent Forms, and Written Subject Information

- 16.1.3.1 IRB Information
- 16.1.3.2 IRB Study Submission Letter English
- 16.1.3.3 IRB Study Submission Letter Japanese
- 16.1.3.4 IRB Study Approval Letter English
- 16.1.3.5 IRB Study Approval Letter Japanese
- 16.1.3.6 IRB Protocol Amendment Submission Letter English
- 16.1.3.7 IRB Protocol Amendment Submission Letter Japanese
- 16.1.3.8 IRB Protocol Amendment Approval Letter English
- 16.1.3.9 IRB Protocol Amendment Approval Letter Japanese
- 16.1.3.10 IRB Subject Information and Informed Consent Form Version 1.0 Submission Letter English
- 16.1.3.11 IRB Subject Information and Informed Consent Form Version 1.0 Submission Letter Japanese
- 16.1.3.12 IRB Subject Information and Informed Consent Form Version 1.0 Approval Letter English
- 16.1.3.13 IRB Subject Information and Informed Consent Form Version 1.0 Approval Letter Japanese
- 16.1.3.14 IRB Subject Information and Informed Consent Form Version 2.0 Submission Letter English
- 16.1.3.15 IRB Subject Information and Informed Consent Form Version 2.0 Submission Letter Japanese



16.1.3.16 IRB Subject Information and Informed Consent Form Version 2.0
Approval Letter English

16.1.3.17 IRB Subject Information and Informed Consent Form Version 2.0
Approval Letter Japanese

16.1.3.18 Subject Information and Informed Consent Form English

16.1.3.19 Subject Information and Informed Consent Form Japanese

16.1.4 List of Investigators and Other Important Participants and Descriptions
of Qualifications and Research Facilities

16.1.4.1 Site 1

16.1.4.2 Site 2

16.1.4.3 CV of Key CRO Staff

16.1.5 List of Subjects Receiving Investigational Products from Specific
Batches, Where More Than One Batch Was Used

Not applicable.

16.1.6 Randomization Scheme and Codes

16.1.7 Audit Certificates

Not applicable.

16.1.8 Documentation of Statistical Methods

16.1.9 Bioanalytical Documentation

16.1.9.1 Standardization and Laboratory Reference Ranges

16.1.9.2 Lab Certificates

16.1.9.3 Bioanalytical Reports

16.1.9.4 Bioanalytical References

16.1.10 Publications Based on the Clinical Study

16.1.11 All Publications Referenced in the Report

16.2 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

Not applicable. No deaths, other serious adverse events, or withdrawal for adverse
events.



16.3 CRF of All Study Participants

16.3.1 Screen Failures

16.3.2 Enrolled and Not Randomized

16.3.3 Randomized

16.4 Individual Subject Data Listings (US Archival Listings)

Not applicable.