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PMI RESEARCH & DEVELOPMENT

Clinical Study Report

ZRHM-REXA-07-JP

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

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

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



SYNOPSIS

Sponsor: Philip 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 randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Principal Investigators and Study Centers: Mamoru Oki, MD PhD Seishukai Clinic 3-18-5, Matsugaya, Taitou-ku, Tokyo 111-0036, Japan Professor Masahiro Endo, MD Tokyo Heart Center Osaki Hospital 5-4-12, Kita-Shinagawa, Shinagawa-ku, Tokyo 141-0001, Japan		
Publication (reference): ClinicalTrials.gov ID: NCT01970995. Reduced Exposure Study Using the Tobacco Heating System 2.2 (THS 2.2) Menthol for 90 Days in Confinement and Ambulatory		
Period of Study: First subject screened: 01 August 2013 Last subject last visit: 03 July 2014		
Objectives and Endpoints: Primary Objectives and Endpoints: The primary objectives and endpoints of this study were: <ol style="list-style-type: none">To demonstrate the reduction of primary biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) (except Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [NNAL]) in a confinement setting in smokers switching from menthol conventional cigarette (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC. <u>Endpoint:</u><ul style="list-style-type: none">Monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), and S-phenylmercapturic acid (S-PMA) in 24-hour urine (concentration adjusted for creatinine), and carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC. <u>Endpoint:</u><ul style="list-style-type: none">Total NNAL level (concentration adjusted for creatinine) in 24-hour urine fraction as measured on		



Day 90 Visit.

Secondary Objectives and Endpoints:

The secondary objectives and endpoints of this study were:

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

Endpoint:

- Number of mCC or THS Menthol Tobacco Sticks smoked daily as reported on the log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.
2. To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoint:

- BoExp listed as secondary (expressed as quantity excreted or concentration adjusted for creatinine) as measured in 24-hour urine on Day 5 and Day 90 Visit.
3. To describe the levels of primary and secondary BoExp over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoints:

- BoExp listed as primary and secondary from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit, and Day 90 Visit as follows:
 - Carbon monoxide ([CO] expressed as ppm) in exhaled breath.
 - Carboxyhemoglobin in blood (expressed as % saturation of hemoglobin).
 - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine.
4. To determine the levels of nicotine over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire Exposure Period.

Endpoints:

- Nicotine equivalents (NEQ; expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
 - Nicotine and cotinine in plasma from Day 1 to Day 5, and on Day 30 Visit, Day 60 Visit, Day 90 Visit.
5. To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints:

- Peak (highest concentration along the day) on Day 5.
 - Time to peak (t_{peak} ; actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
 - Weighted average concentration over 24 hours (C_{avg}) on Day 5.
6. To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.

**Endpoint:**

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

7. To monitor the safety profiles during the study.**Endpoints:**

- 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 one open question.
 - Vital signs.
 - Spirometry.
 - Electrocardiogram (ECG).
 - Clinical chemistry, hematology, and urine analysis safety panel.
 - Physical examination.
 - Concomitant medications.
8. To monitor selected risk markers (CREs) in a confinement and ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoints:

- Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TGs), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
- Soluble intercellular adhesion molecule-1 (sICAM-1) in serum on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- White blood cell (WBC) and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-prostaglandin F2 alpha (8-epi-PGF_{2α}) and 11-dehydro-thromboxane B2 (11 DTX-B2) in 24-hour urine on Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
- Body weight and waist circumference on Day 90 Visit.

Exploratory Objectives and Endpoints:

The exploratory objectives and endpoints of this study were:

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

Endpoints:

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



questionnaire: score from FTND questionnaire on the Day 90 Visit.

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

Endpoints:

- BoExp for the primary and secondary objectives on Day 5 and on Day 90 Visit in 24-hour urine.
- Selected risk markers (CREs; hs-CRP, homocysteine, blood glucose, LDL cholesterol, HDL cholesterol, TG, TC, fibrinogen, HbA1c, sICAM-1, WBC, platelet count, 8-epi-PGF_{2α}, 11-DTX-B2) in respective body matrix when available on Day 5 and Day 90 Visit.

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

Endpoints:

- Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
- Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.

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

Endpoints:

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

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

Endpoint:

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

Methodology:

Study design:

This was a randomized, controlled, open-label, 3-arm parallel group multi-center study to compare the use of THS 2.2 Menthol with continuing to smoke mCC, and SA. This was an *ad libitum* smoking study with no restriction on product use in the THS 2.2 Menthol and mCC arms for the Ambulatory Setting.

Screening Period: Day -30 to Day -3:

The Screening Period covered 4 weeks prior to Admission to the clinic (Day -2). A demonstration of the THS 2.2 Menthol product was given to the subject during the Screening Visit. Subjects were in a confined setting for 9 days from Day -2 onwards.

Run-in Period: Day -2 (Admission) until Day -1, 06:29 AM:

Prior to enrollment on Day -2, as the last procedure of the eligibility assessments, subjects had a product test of the THS 2.2 Menthol (using up to 3 THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product test was performed only when the urine pregnancy test was negative. Enrollment took place after all inclusion and exclusion criteria had been satisfactorily met. Only subjects willing and able to use the product were enrolled.

All subjects participating in the product trial on Day -2 who were not enrolled into the study entered a 28-day safety Follow-up Period.

Baseline Period: Day -1, 06:30 AM until Day 1, 06:29 AM:

The Baseline Period was defined as from 06:30 AM on Day -1 until 06:29 AM on Day 1. All subjects



continued smoking their single preferred brand of mCC and baseline values were recorded. On Day 0, subjects were randomized to one of the 3 study arms in a 2:1:1 ratio using a stratified randomization by sex and average daily mCC consumption over the last 4 weeks as reported during the Screening Visit. Subjects were informed of their randomized study arm by the study collaborators on Day 1 prior to 06:30 AM.

Exposure Period:

For the analyses, the period of exposure was separated in the following way: Period 1 [Day 1 - Day 6 Confinement]; Period 2 [Day 6 Ambulatory – Day 30 Visit]; Period 3 [Day 30 Visit – Day 60 Visit]; and Period 4 [Day 60 Visit – Day 90 Visit].

Exposure Period in Confinement: Day 1, 06:30 AM, until Discharge on Day 6

Subjects who were allocated to THS 2.2 Menthol and mCC arms used their assigned product *ad libitum* for 5 days. Subjects allocated to the SA arm were asked to abstain from smoking. During the period of SA, subjects were provided psychological support, but were not provided with smoking cessation medications. Product use during the Confinement Period was allowed between 06:30 AM and 11:00 PM. Twenty-four-hour urine was collected from Day -1 to the morning of Day 6 on site.

Exposure period in the Ambulatory Setting: Discharge on Day 6 until 11:00 PM on Day 90:

After Discharge on Day 6, subjects were instructed to continue their assigned product/regimen in an ambulatory setting for 85 days. Subjects were allowed to use nicotine replacement therapy (NRT) if considered necessary by the Principal Investigator or requested by the subject.

Subjects were required to make 3 Ambulatory Visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each visit covered 2 consecutive days on site. For Ambulatory Visits, the subject checked in at approximately 08:00 AM, and checked-out the next day. Twenty-four-hour urine was collected at each Ambulatory Visit at the site with the sample collection spanning 2 days. For example, urine was collected from 09:00 AM on Day 90 and the end of the 24-hour urine collection for the Day 90 Visit ended in the morning of Day 91 at 08:59 AM (± 20 minutes).

Product use on Ambulatory Visits was unrestricted, and subjects in the THS 2.2 Menthol and mCC arms were allowed to use their assigned product from approximately 08:00 AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31 and Day 61, product use was allowed from 06:30 AM. The last exposure to the allocated product was at Day 90, 11:00 PM. On Day 91, subjects were discharged from the investigational site after all safety examination procedures had been conducted.

Safety Follow-up Period: From Discharge on Day 91 (or another day for subjects who discontinued early) until Day 119:

After Discharge on Day 91, subjects entered a 28-day safety Follow-up Period during which the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs was performed by the study site. In general, all AEs were to be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event had been found. The end of the study was defined as the end of the 28-day follow-up.

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

Number of Subjects (Planned and Analyzed):

Planned:	160 subjects
Screened:	670 subjects
Enrolled:	231 subjects
Discontinued due to ICH/GCP non-compliance at Seishukai Clinic:	56 subjects
Safety Population (Tokyo Heart Center):	175 subjects
Subjects who were enrolled and not randomized:	15 subjects



Randomized (Tokyo Heart Center):	160 subjects
Safety Population (Tokyo Heart Center, post-randomization):	160 subjects
Full Analysis Set (FAS) population:	160 subjects
<u>Per Protocol (PP) Set Populations:</u>	
PP Population Period 1:	157 subjects
PP Population Period 2:	154 subjects
PP Population Period 3:	150 subjects
PP Population Period 4:	148 subjects
<u>Compliant Populations:</u>	
Compliant Population Period 1:	157 subjects
Compliant Population Period 2:	142 subjects
Compliant Population Period 3:	144 subjects
Compliant Population Period 4:	143 subjects
Diagnosis and Main Criteria for Inclusion:	
One hundred and sixty female or male smoking healthy Japanese subjects who met the following main inclusion criteria were planned to be enrolled:	
<ul style="list-style-type: none">• Subject has signed the informed consent form (ICF) and was able to understand the information provided in the Subject Information Sheet and ICF.• Subject was aged from 23 to 65 years (inclusive).• Subject was Japanese.• Smoking, healthy subject as judged by the Principal Investigator based on all available assessments from 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 spirometry, post-bronchodilator FEV₁ >80% pred value, and post-bronchodilator FVC >80% pred value], vital signs, physical examination, ECG, chest X-ray, and medical history).• Subject smoked at least 10 commercially available mCCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine International Organization of 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 ready to accept interruptions of smoking for up to 90 days.• The subject was ready to accept using the THS 2.2 Menthol.	
Subjects who did not complete the study after randomization were not replaced.	
Test Product and Lot Numbers:	
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 mains power supply, and a USB cable.	
Pack batch number of THS Menthol Tobacco Sticks: B-05775, Production date: 12-Jun-2013, Expiry date: 11-Mar-2014; and B-08544, Production date: 25-Oct-2013, Expiry date: 24-Jul-2014.	
Duration of Exposure Period:	
The Exposure Period was approximately 90 days and was from Day 1, 06:30 AM, until 11:00 PM on Day 90. Day of Discharge was defined as Day 90, 11:00 PM, until Discharge on Day 91. The Exposure Period included both the Exposure Period in Confinement and the Exposure Period in the Ambulatory Setting. Product use periods were subsets of the Exposure Period and were defined as Period 1, Period 2, Period 3, and Period 4.	
Reference Products:	
The reference product during the randomized Exposure Period was the subject's own preferred commercially available single brand of mCC. Smoking abstinence was also included in this study as a	



frame of reference.

Statistical Methods:**Analysis Populations:**

The PP Set was the primary analysis data set for BoExp, CREs, and questionnaire assessments. The FAS was the primary analysis data set for compliance to randomization arm. Subjects enrolled at the Seishukai Clinic were discontinued due to the site being found to be non-compliant with ICH/GCP guidance and thus, were excluded from the FAS/PP and the Safety Population; however, they were reported within the Full Safety Population. The Compliant Population was a subset of subjects from the PP Set; for the THS 2.2 Menthol arm it included subjects who were exclusive THS 2.2 Menthol users, for the mCC arm it included subjects who were exclusive users of mCC, and for the SA arm it included subjects who were fully abstinent.

Primary Analyses:

The BoExp included as endpoints in the primary objective and assessed on Day 5 for the comparison of THS 2.2 Menthol and mCC in a confinement setting were MHBMA, 3-HPMA, S-PMA (concentration adjusted for creatinine) in 24-hour urine, and COHb in blood (expressed as % saturation of hemoglobin). The BoExp included as endpoints in the primary objective and assessed for the comparison of THS 2.2 Menthol and mCC in an ambulatory setting was Total NNAL (adjusted for creatinine) in 24-hour urine as measured at the Day 90 Visit.

The endpoints included in the primary objectives were log-transformed (base_e) prior to analysis. An analysis of covariance (ANCOVA) model was used with terms for the log-transformed baseline value, stratification factors, and randomization arm. The least squares (LS) means and estimate of the difference were back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), two-sided 95% confidence interval (CI) and one-sided p-value were tabulated. These analyses were performed on the PP Set, the FAS, and the Compliant Population. A sensitivity analysis was also performed on the PP Set using a mixed model approach (conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors).

Descriptive summary statistics including the number of subjects (n), the number and percentage of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), 95% CI, median, first and third quartiles, minimum, and maximum; for log-normal data the geometric mean, geometric 95% CI, and geometric coefficient of variance (CV) were also tabulated for each study arm, for the PP Set, Compliant Population, and FAS. In addition, BoExp included as endpoints in the primary objective endpoints were summarized, stratified by sex and mCC consumption over the last 4 weeks as reported during the Screening Visit, for the PP Set.

Secondary Analyses:

The BoExp included as endpoints in the primary objective were analyzed in the secondary objectives at Day 5 for Total NNAL and Day 90 for COHb, MHBMA, 3-HPMA, and S-PMA, for the PP Set and FAS using the same methodology as for the primary analysis, including the sensitivity analysis. The BoExp were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as for the primary analysis for the PP Set.

The BoExp included as endpoints in the secondary objectives were exhaled CO and Total 1-hydroxypyrene (1-OHP), Total N-nitrosornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxybenzo(a)pyrene (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), S-benzylmercapturic acid (S-BMA), and NEQ (all analyzed from a 24-hour urine collection) on Day 5 and Day 90 to compare reductions in THS 2.2 Menthol versus mCC and versus SA. All analyses as described above were performed on the concentrations adjusted for creatinine and for the quantity excreted in urine over 24 hours.

Biomarkers of exposure were analyzed using the same model described for the primary analysis (including



the sensitivity analyses) versus mCC and versus SA. Carbon monoxide was analyzed on the linear scale and arithmetic means were calculated; whereas other BoExp were analyzed on the logarithmic scale to calculate geometric means. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the statistical significance was evaluated for the results of the Day 90 analysis. Least squares means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated.

Nicotine and cotinine concentrations at each post-baseline time point were analyzed in the log space using an ANCOVA model with terms for log-transformed baseline concentration, stratification factors, and randomization arm. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated. All figures, summaries, and analyses were performed using the PP Set and FAS.

The peak nicotine and cotinine plasma concentration (C_{peak}) and time to peak concentration (t_{peak}) were obtained directly from the concentrations taken on Day 5. The weighted average concentration over 24 hours on Day 5 (C_{avg}) was calculated by dividing the area under the curve from 0 to 24 hours (AUC_{0-24h}) by 24, where the AUC_{0-24h} was calculated using the linear trapezoidal rule.

The analysis compared the log-transformed C_{peak} and C_{avg} on Day 5 between the THS 2.2 Menthol and mCC arms. An analysis of variance (ANOVA) model was used with terms for stratification factors, and randomization arm. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were generated.

For t_{peak} on Day 5, the comparison between the THS 2.2 Menthol and mCC arms was made by the Wilcoxon Rank Sum test. Median difference and 95% CI using the Hodges-Lehmann estimate were tabulated.

All PK parameter summaries and analyses were performed using the PP Set and FAS as defined above.

For assessment of product compliance and extent of exposure, daily product use during the Confinement Period was recorded in a log and was summarized by randomization arm. In addition, in the SA arm, the levels of CO in exhaled breath (continuous and categorical) were summarized and listed. During the Ambulatory Period, the daily product use (e.g., menthol and non-menthol conventional cigarettes [CC], THS Menthol Tobacco Sticks) was recorded in electronic diaries and was summarized by randomization arm and by product use categorization. In addition, the number and percentage of subjects falling into each product use category during the Ambulatory Period were tabulated.

For CYP1A2 activity, the analysis compared the log-transformed Day 5 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms using an ANOVA model. If the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the analysis was repeated for the Day 90 values. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated. All CYP1A2 summaries and analyses were performed using the PP Set and FAS.

For analysis of CREs, the results along with the changes from baseline were listed and summarized. In addition, line graphs were produced for product means (and 95% CI) over all time points. The analysis compared the results on Days 5, 30, 60, and 90 Visits, as applicable, between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms for the PP Set and FAS. An ANCOVA model was used with terms for baseline result, stratification factors, and randomization arm. If applicable and there was evidence of non-normality, the results were log-transformed prior to analysis. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) or ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated along with a forest plot of the results. Although FEV_1 was not analyzed as a CRE in the protocol and therefore the analysis was not planned prior to the locking of the database, PMI considers FEV_1 to be a CRE and therefore a posthoc analysis was performed for the FEV_1 parameter following the same approach as for other CREs.

For the MCEQ, each item was assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). The subscale scores were derived by averaging the individual non-missing item scores if at least 50% of the items within a subscale were non-missing, otherwise the subscale score was set to missing. As the



questionnaire is intended to evaluate use of tobacco products (THS 2.2 or mCC), summaries, profiles, and analysis only included the THS 2.2 Menthol and mCC arms. The change from baseline was calculated for the 5 subscale scores. The subscale scores, along with the change from baseline were summarized. Profiles of the raw means from baseline to Day 90 for the 5 subscale scores were produced. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) with 95% CI were presented.

Least squares means for each HST parameter per-cigarette along with the difference (THS 2.2 Menthol - mCC) with 95% CI were presented at all assessed time points in the study. Visual inspection of THS Tobacco Plugs was also performed on Days 1 to 5 of the Confinement Period, and on Ambulatory Visits. The number and percentage of tobacco plugs showing each of the following criteria were summarized by day: "No overheating"; "White spot(s) inside the tobacco plug"; Ashes inside the tobacco plug and burnt"; and "Missing".

Study Hypotheses and Evaluation Criteria

The hypothesis tested was that the geometric mean level of the BoExp for THS 2.2 Menthol were lower relative to mCC. For BoExp included as endpoints in the primary objective, the hypothesis was tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and on Day 90 Visit for Total NNAL. The secondary objectives tested the BoExp included as endpoints in the primary objective and the remaining BoExp. If the hypothesis test was significant at Day 5 then the endpoint was further tested Day 90.

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

Safety Analyses:

All safety analyses were presented by the Safety Population. Adverse events were categorized by system organ class (SOC) and preferred term (PT) and coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 16.0). Respiratory symptoms (cough assessment questionnaire), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), spirometry, ECG data, clinical laboratory safety parameters (clinical chemistry, hematology, and urine analysis), body mass index, physical examination, and device malfunction/misuse events were summarized.

All medications were listed using PT and Anatomical, Therapeutic, and Chemical (ATC) codes (World Health Organization-Drug Dictionary, Q1 2013). Concomitant medications were summarized by randomization arm for the Safety Population showing the number and percent of subjects who used the medication at least once by actual exposure and by ATC first and second levels and by preferred drug name.

All data for the Full Safety Population were listed.

**Summary of Results****Primary Objectives and Endpoints Analyses**

The primary objectives for this study assessed on Day 5 the BoExp COHb in blood (expressed as % saturation of hemoglobin); and the following BoExp expressed as urinary concentration adjusted for creatinine in urine: MHBMA (pg/mg creat); 3-HPMA (ng/mg creat); and S-PMA (pg/mg creat); and on Day 90 Total NNAL expressed as urinary concentration adjusted for creatinine in urine (pg/mg creat).

Reductions were observed in the level of each BoExp assessed for the THS 2.2 Menthol arm compared to the mCC arm on Day 5, with reductions of 55% (95% CI: 52.0, 57.9) in COHb, 87% (95% CI: 83.4, 89.0) in MHBMA, 49% (95% CI: 42.8, 55.1) in 3-HPMA, and 89% (95% CI: 87.0, 90.7) in S-PMA. In addition, on Day 90, a reduction of 77% (95% CI: 68.9, 82.6) was observed in the level of Total NNAL.

For all of the BoExp included in the analysis of the primary objective at their respective time points, the study showed a reduction in smokers that switch to THS 2.2 Menthol compared to smokers that continued to smoke mCC. This reduction was 50% or more for COHb, MHBMA, Total NNAL, and S-PMA. A 49% reduction was observed in 3-HPMA while achieving levels consistent with the expected effect compared to SA.

Secondary Objectives and Endpoints Analyses

Carboxyhemoglobin in Whole Blood, 3-HPMA, MHBMA, S-PMA, and Total NNAL (Concentrations Adjusted for Creatinine) versus Smoking Abstinence and Menthol Conventional Cigarettes on Day 5 (Confinement Period) and on Day 90 (Ambulatory Period)

Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 and on Day 90 versus mCC and versus SA (PP Set)				
Biomarker/ Time point	Ratio THS m2.2:mCC		Ratio THS m2.2:SA	
	%	95% CI	%	95% CI
Evening COHb (%)				
Day 5	44.94	42.11, 47.97	99.31	92.91, 106.15
Day 90	51.72	48.07, 55.65	97.10	90.03, 104.72
Urinary MHBMA (pg/mg creat)				
Day 5	13.49	10.96, 16.60	99.57	80.56, 123.06
Day 90	19.01	14.68, 24.61	101.34	77.68, 132.20
Urinary 3-HPMA (ng/mg creat)				
Day 5	50.67	44.88, 57.20	165.87	146.50, 187.81
Day 90	54.08	46.94, 62.32	138.52	119.70, 160.30
Urinary S-PMA (pg/mg creat)				
Day 5	10.97	9.26, 12.99	113.70	95.67, 135.12
Day 90	12.80	9.88, 16.58	98.78	75.68, 128.94
Urinary Total NNAL (pg/mg creat)				
Day 5	43.69	39.62, 48.17	119.61	108.23, 132.19
Day 90	23.25	17.38, 31.11	150.85	111.62, 203.87
Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; mCC = menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.				

The reductions in COHb, 3-HPMA, MHBMA, and S-PMA observed on Day 5 during the Confinement Period for the THS 2.2 Menthol arm compared to the mCC arm were sustained during the Ambulatory Period, with decreases of 48% in COHb, 81% in MHBMA, 46% in 3-HPMA, and 87% in S-PMA, evident



on Day 90. In addition, the reductions observed on Day 90 for Total NNAL were apparent on Day 5, with levels reduced by 56% in the THS 2.2 Menthol arm compared to the mCC arm.

There were no notable differences observed on Day 5 or Day 90 between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking for COHb, MHBMA, and S-PMA.

The levels of 3-HPMA and Total NNAL were higher for the THS 2.2 Menthol arm compared to the SA arm; 66% higher on Day 5 and 39% higher on Day 90 for 3-HPMA; and 20% higher on Day 5 and 51% higher on Day 90 for Total NNAL. Although, the numerical difference between the THS 2.2 Menthol and SA arms appeared substantial; when in the context of the reduction from mCC, THS 2.2 Menthol preserved most of the effect observed in the SA arm.

Other Biomarkers of Exposure (Exhaled CO [ppm] and Other Urinary Biomarkers of Exposure [Concentration Adjusted for Creatinine]) versus Menthol Conventional Cigarettes and Smoking Abstinence in the Confinement Period and Ambulatory Period

Analysis of Other Biomarkers of Exposure on Day 5 and on Day 90 versus mCC and versus SA (PP Set)

Biomarker/ Time point	Ratio THS m2.2:mCC		Ratio THS m2.2:SA	
	%	95% CI	%	95% CI
Urinary Total 1-OHP (pg/mg creat)				
Day 5	39.18	34.82, 44.07	109.65	97.23, 123.66
Day 90	52.02	44.83, 60.38	94.78	81.31, 110.48
Urinary Total NNN (pg/mg creat)				
Day 5	27.02	21.75, 33.55	786.46	630.18, 981.50
Day 90	29.31	21.48, 39.98	488.54	354.58, 673.12
Urinary 4-ABP (pg/mg creat)				
Day 5	20.10	17.08, 23.64	86.22	72.93, 101.94
Day 90	21.00	17.02, 25.89	85.76	69.00, 106.60
Urinary 1-NA (pg/mg creat)				
Day 5	5.70	4.93, 6.59	104.70	90.26, 121.44
Day 90	6.22	4.70, 8.22	81.26	60.87, 108.47
Urinary 2-NA (pg/mg creat)				
Day 5	13.66	12.04, 15.49	91.67	80.53, 104.33
Day 90	15.45	12.98, 18.39	85.50	71.35, 102.45
Urinary o-tol (pg/mg creat)				
Day 5	43.80	36.31, 52.83	102.80	85.37, 123.79
Day 90	59.16	42.02, 83.29	87.24	61.98, 122.80
Urinary CEMA (ng/mg creat)				
Day 5	18.23	16.16, 20.56	107.03	94.63, 121.05
Day 90	9.17	7.01, 12.00	91.93	69.65, 121.33
Urinary HEMA (pg/mg creat)				
Day 5	50.14	44.09, 57.02	102.15	89.55, 116.51
Day 90	44.96	37.17, 54.37	102.01	83.82, 124.15
Urinary B[a]P (fg/mg creat)				
Day 5	27.19	23.17, 31.91	110.59	93.84, 130.33
Day 90	33.02	25.92, 42.08	95.92	74.58, 123.38



Urinary HMPMA (ng/mg creat)				
Day 5	43.06	37.75, 49.10	109.54	95.76, 125.30
Day 90	50.31	42.96, 58.91	95.90	81.47, 112.89
Urinary S-BMA (pg/mg creat)				
Day 5	85.83	76.49, 96.31	94.56	84.06, 106.38
Day 90	111.27	88.65, 139.67	91.73	72.53, 116.01
<p>Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 4-ABP = 4-aminobiphenyl; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CO = carbon monoxide; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = menthol conventional cigarettes; NNN = N-nitrosornicotine; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol</p> <p>Note: The difference in exhaled CO was calculated for THS 2.2 Menthol versus mCC or SA rather than the geometric LS mean ratio: Day 5 -13.10 (-14.70, -11.50) versus mCC and -0.85 (-2.49, 0.79) versus SA; Day 90 -9.28 (-10.75, -7.81) versus mCC and -0.23 (-1.75, 1.29) versus SA.</p>				

Reductions observed in the THS 2.2 Menthol arm compared to the mCC arm (excluding S-BMA) ranged from 41% for o-toluidine to 94% for 1-NA.

Levels of the BoExp observed in subjects who switched to THS 2.2 Menthol use approached levels measured in subjects who abstained from smoking, except for Total NNN, which was 8-fold and 5-fold higher in the THS 2.2 Menthol arm compared to the SA arm on Day 5 and Day 90, respectively. Although, the numerical difference between the THS 2.2 Menthol and SA arms appeared substantial, when analyzed in the context of the reduction from mCC, THS 2.2 Menthol preserved most of the effect observed in the SA arm.

Levels of S-BMA at Day 90 were comparable between subjects who switched to THS 2.2 Menthol use, subjects who continued smoking mCC, and subjects who abstained from smoking; and throughout the study S-BMA appeared to be unsuitable to discriminate between smokers and non-smokers.

Exposure to Nicotine (Concentrations and Pharmacokinetic Profiles) in Confinement Period and in Ambulatory Period

The NEQ urinary concentration adjusted for creatinine in the THS 2.2 Menthol arm initially decreased at Day 1 compared to baseline (-6.26%) and then increased from Day 1 to Day 5. On Day 5, NEQ urinary concentration adjusted for creatinine was approximately 16% (95% CI: -1.1, 36.0) higher in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC. This difference progressively reduced over time and on Day 90 the NEQ was comparable between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC (104%; 95% CI: 66.7, 163.2).

A similar trend was observed for nicotine and cotinine concentrations in plasma. On Day 5, the levels of nicotine and cotinine between 08:00 PM and 09:30 PM were 10% and 12% higher, respectively, in the THS 2.2 Menthol arm compared to the mCC arm (95% CI: -7.9, 32.3 for nicotine; and 95% CI: -0.13, 24.8 for cotinine). These differences decreased over time, starting from Day 60. There were no notable differences in evening plasma nicotine or cotinine levels in the THS 2.2 Menthol arm compared to the mCC arm on Day 90 (nicotine: 103%; 95% CI: 82.7, 129.3; cotinine: 106%; 95% CI: 89.9, 124.8). For the nicotine PK profile on Day 5, peak plasma concentrations were 31% (95% CI: 6.9, 59.6; 20.70 ng/mL for THS 2.2 Menthol arm and 15.67 ng/mL for mCC arm) higher in the THS 2.2 Menthol arm compared to mCC arm, and weighted average concentrations were 27% (95% CI: 1.3, 59.2; 11.20 ng/mL for THS 2.2 Menthol arm and 8.72 ng/mL for the mCC arm) higher in the THS 2.2 Menthol arm compared to mCC arm. For cotinine PK profile on Day 5, peak and weighted average plasma concentrations were 17% (95% CI: -5.1, 44.2; 192.10 ng/mL for the THS 2.2 Menthol arm and 163.42 ng/mL for the mCC arm) and 16% (95% CI: -6.3, 42.4; 171.25 ng/mL for the THS 2.2 Menthol arm and 147.39 ng/mL for the mCC arm) higher, respectively,



for the THS 2.2 Menthol arm compared to the mCC arm. The median time to peak concentration on Day 5 was identical for the THS 2.2 Menthol and mCC arms for both nicotine (12 hours) and cotinine (16 hours).

Cytochrome P450 1A2 Activity

On Day 5, CYP1A2 activity had decreased from baseline by 22% and 24% in the THS 2.2 Menthol and SA arms, respectively; while in the mCC arm, CYP1A2 activity was 10% higher than baseline. During the Ambulatory Period, CYP1A2 activity remained decreased with a 20% and 16% change from baseline in the THS 2.2 Menthol and SA arms, respectively, and increase from baseline in the mCC arm of 16% on Day 90.

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 28% (95% CI: 22.8, 32.9) lower than in subjects who continued to smoke mCC on Day 5, which was sustained during the Ambulatory Period with CYP1A2 activity 31% (95% CI: 22.3, 38.6) lower than mCC on Day 90. There was no notable difference in CYP1A2 activity between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102%; 95% CI: 95.4, 110.0 on Day 5; 93%; 95% CI: 82.0, 104.4 on Day 90).

Extent of Exposure – Product Use Consumption

At baseline (Day 0), the mean (95% CI) number of mCC consumed daily in the THS 2.2 Menthol and mCC arms (PP Set Period 1) was 13.1 (95% CI: 12, 14) and 12.5 (95% CI: 11, 14) mCC/day, respectively. During the Confinement Period, the number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm was lower than the number of mCC smoked at baseline with a mean of 11.4 (95% CI: 11, 12) sticks/day on Day 1 and then increased over the Confinement Period to 14.0 (95% CI: 13, 15) sticks/day on Day 5. Similarly, the daily consumption of mCC in the mCC arm decreased compared to baseline, with a mean of 11.0 (95% CI: 10, 12) mCC/day on Day 1, and then increased to 13.6 (95% CI: 12, 15) mCC/day on Day 5.

During the Ambulatory Period, the mean number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm returned to similar levels as baseline, with a mean 11.7 (95% CI: 10.2, 13.1), 12.7 (95% CI: 11.1, 14.2), and 12.7 (95% CI: 11.2, 14.3) sticks/day reported during PP Set Periods 2, 3, and 4, respectively. In the mCC arm, the mean number of mCC consumed daily during the Ambulatory Period remained higher as compared to baseline, with a mean 15.2 mCC/day (95% CI: 13.5, 16.8) reported during PP Set Period 4. For each product use period in the Ambulatory Period, the mean reported daily number of THS Menthol Tobacco Sticks was lower than the daily product use in the mCC arm.

In the THS 2.2 Menthol arm, the use of mCC was negligible and the combined daily use of mCC and THS 2.2 Menthol over the Ambulatory Period was lower than the daily product use in the mCC arm.

The results for the PP Sets Periods 1, 2, 3, and 4 were similar to the Safety Population in each period.

Compliance to Product Use (FAS Population)

During the Confinement Period, as product use/regimen was fully controlled, 100% of subjects in each study arm (i.e., THS 2.2 Menthol, mCC, and SA) were compliant with their product regimen.

During the Ambulatory Period, in the THS 2.2 Menthol study arm at least 82.1% of subjects in each period exclusively used the assigned THS 2.2 Menthol product (100%). More than 85.9% of subjects in each period were classified as primarily THS 2.2 Menthol users (>95% of THS 2.2 Menthol arm). In the mCC arm all 41 subjects who completed the study, used the assigned product exclusively in each period, and in the SA study arm at least 92.5% remained abstinent in each period.

Risk Markers (Clinical Risk Markers)

- *Risk Marker of Oxidative Stress: 8-epi-PGF_{2α} (Concentration Adjusted for Creatinine) (Day 90)*

The levels of 8-epi-PGF_{2α} in subjects who switched to THS 2.2 Menthol were 12.7% (95% CI: 2.55, 21.81) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (92.8% ratio; 95% CI: 82.80, 103.96).

- *Risk Marker of Platelet Activation: 11-DTX-B2 (Concentration Adjusted for Creatinine) (Day 90)*



The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 9.0% (95% CI: -2.94, 19.52) lower than that observed in subjects who continued to smoke mCC. The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 13% (95% CI: -0.53, 28.12) higher than that observed in subjects who abstained from smoking.

- *Risk Marker of Endothelial Dysfunction: sICAM-1 (Day 90)*

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol use were 8.7% (95% CI: 2.05, 14.94) lower than that observed in subjects who continued to smoke mCC. There were no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102.4% ratio; 95% CI: 95.24, 110.12).

- *Risk Markers of Lipid Metabolism: LDL Cholesterol, HDL Cholesterol, Triglycerides, and Total Cholesterol (Day 90/Day of Discharge from Ambulatory Period)*

The HDL cholesterol levels were increased by approximately 4.5 mg/dL (95% CI: 1.17, 7.88) in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-1.8 difference; 95% CI: -5.28, 1.61).

For TGs, there were no notable differences observed between subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (-6.3 mg/dL difference; 95% CI: -21.20, 8.69). The levels in subjects who switched to THS 2.2 Menthol use was 18.7 mg/dL (95% CI: 2.99, 34.39) lower than in subjects who abstained from smoking.

There were no notable differences observed in the levels of TC or LDL cholesterol between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and compared to subjects who abstained from smoking.

- *Risk Markers of Inflammation: Platelets and White Blood Cell Differential Counts (Day of Discharge from Ambulatory Period)*

There were no notable differences observed in platelet counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (102.9% ratio; 95% CI: 97.61, 108.57). The platelet counts were 6.2% (95% CI: 0.56, 12.28) higher in subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking.

Total WBC (leukocytes) counts in subjects who switched to THS 2.2 Menthol use were 0.6 GI/L (95% CI: 0.10, 1.04) lower than that observed in subjects who continued to smoke mCC. There were no notable differences observed in the leukocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.2 difference; 95% CI: -0.65, 0.33).

Neutrophils counts in subjects who switched to THS 2.2 Menthol use was 0.5 GI/L (95% CI: 0.08, 0.88) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.1 difference; 95% CI: -0.48 0.35).

Monocyte counts in subjects who switched to THS 2.2 Menthol use were 0.1 GI/L (95% CI: 0.01, 0.10) lower than that observed in subjects who continued to smoke mCC. There were no notable differences observed in the monocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking.

For lymphocytes, monocytes, eosinophils, and basophils there were no notable differences observed in counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC and compared to subjects who abstained from smoking.

- *Cardiovascular Risk: Homocysteine, hs-CRP, and Fibrinogen (Day 90)*

For homocysteine and fibrinogen, there were no notable differences observed between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and subjects who abstained from smoking.

There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who



continued to smoke mCC for hs-CRP (93.6%; 95% CI: 62.23, 140.75). The levels of hs-CRP in subjects who switched to THS 2.2 Menthol use was 10.7% (95% CI: -27.33, 68.76) higher than that observed in subjects who abstained from smoking.

- *Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure (Day of Discharge from Ambulatory Period)*

There were no notable differences observed in the systolic and diastolic blood pressure for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCCs, and compared to subjects who abstained from smoking.

- *Risk Markers of Metabolic Syndrome: Blood Glucose, Body Weight and Waist Circumference, and Hb1Ac (Day 90/Day of Discharge from Ambulatory Period)*

For glucose, there were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (98.98% ratio; 95% CI: 96.42, 101.60). The levels of glucose in subjects who switched to THS 2.2 Menthol use was 2.80% (95% CI: 0.06, 5.61) higher than that observed in subjects who abstained from smoking.

For Hb1Ac, there were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC and compared to subjects who abstained from smoking.

For assessment of weight, there was no notable difference for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (-0.09 difference; 95% CI: -0.75, 0.57). The values in subjects who switched to THS 2.2 Menthol use were 1.24 kg (95% CI: 0.56, 1.92) lower than in subjects who abstained from smoking.

There were no notable differences observed in waist circumference between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC subjects who switched to THS 2.2 Menthol use and compared with subjects who abstained from smoking.

- *Risk Markers Associated with Respiratory Diseases*

The value of FEV₁ (without bronchodilator) in subjects who switched to THS 2.2 Menthol use were 1.91 %pred (95% CI: -0.14, 3.97) higher than that observed in subjects who continued to smoke mCC. There were no notable differences observed in FEV₁ between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.02 difference; 95% CI: -2.15, 2.11).

Exploratory Endpoint: Product Evaluation Questionnaire (MCEQ)

For craving, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, decreases from baseline were observed as early as Day 1 in the THS 2.2 Menthol arm, ranging from -3.4% (95% CI: -16.41, 9.60) to -23.8% (95% CI: -30.33, -17.18); whereas changes from baseline observed in the mCC arm ranged from 10.8% (95% CI: -1.11, 22.67) to -3.3% (95% CI: -10.44, 3.81). For the aversion subscale, a 16.3% (95% CI: 0.83, 31.69) increase from baseline was observed on Day 1 for the THS 2.2 Menthol study arm, and a 7.8% (95% CI: -10.35, 25.90) increase from baseline was observed on Day 1 for the mCC study arm.

Difference Between THS m2.2 and mCC Scores for MCEQ Subscales – PP Set		
MCEQ Subscale/ Time point	Difference THS m2.2 - mCC	
	Difference	95% CI
Aversion		
Day 1	0.07	-0.24, 0.37
Day 5	0.07	-0.23, 0.37
Day 90	-0.16	-0.49, 0.18
Craving reduction		
Day 1	-0.54	-1.05, -0.03
Day 5	-0.02	-0.55, 0.50



Day 90	-0.15	-0.62, 0.32
Enjoyment of respiratory tract sensation		
Day 1	-0.56	-0.96, -0.16
Day 5	-0.13	-0.55, 0.29
Day 90	0.30	-0.18, 0.78
Psychological reward		
Day 1	-0.41	-0.72, -0.10
Day 5	-0.21	-0.51, 0.10
Day 90	0.00	-0.37, 0.36
Smoking satisfaction		
Day 1	-0.86	-1.26, -0.47
Day 5	-0.39	-0.81, 0.03
Day 90	0.01	-0.39, 0.41
Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.		

On Day 1, the mean scores for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales were lower in subjects who switched to THS 2.2 Menthol use compared to those observed in subjects who continued to smoke mCC (THS m2.2 – mCC difference: -0.5 for craving reduction; -0.6 for enjoyment respiratory tract sensation; -0.4 for psychological reward; -0.9 for smoking satisfaction). By the end of the Exposure Period the THS 2.2 Menthol and mCC arm differences became less for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, with differences on Day 5 of -0.02, -0.13, -0.21, and -0.39, respectively, and differences on Day 90 of -0.15, 0.30, 0.00, and 0.01, respectively.

On Days 5 and 90, there were no notable differences between subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC for aversion subscale.

Exploratory Endpoint: Human Smoking Topography (Day 90)

The total puff volume was similar between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (-23.5 mL difference; 95% CI: -141.54, 94.61). The total smoking duration was approximately 3.4 minutes for both arms (1.84 s difference; 95% CI: -35.93, 32.24) while an increase in puff frequency of 1.03 puffs/min (95% CI: 0.11, 1.94) was observed in subjects using THS 2.2 Menthol use in comparison with subjects who continued to smoke mCC.

An 8.46 mL/s (95% CI: 4.98, 11.94) lower average flow was found in THS 2.2 Menthol, with a 0.26 s (95% CI: -0.02, 0.54) longer average puff duration.

This was the result of an adaptation process for subjects using THS 2.2 Menthol who, compared to subjects in the mCC arm, increased the total number of puffs (3.19 puffs difference; 95% CI: 0.49, 5.89) and compensated with a 9.67 mL (95% CI: 3.48, 15.87) lower average puff volume.

**Safety:**

There were no SAEs or severe AEs reported in this study and no randomized subjects were discontinued due to an AE. Prior to randomization, 15 subjects were discontinued from the study, of which 2 subjects were discontinued due to an AE. In addition, 56 subjects were excluded from the Safety and FAS populations due to premature termination of the site where the subjects were enrolled.

Overall, there were 93 AEs reported post-randomization by 60 of the 160 subjects (37.5%) in the Safety Population, most of which were mild in severity. Only 2 AEs were considered moderate, with 1 moderate AE reported in the Confinement Period for the SA arm and 1 moderate AE reported in the Ambulatory Period for the mCC arm. The number of subjects reporting AEs in each study arm were 32/78 (41.0%) for the THS 2.2 Menthol arm, 14/42 (33.3%) for the mCC arm, and 14/40 (35.0%) for the SA arm.

Only 1 AE reported was considered to be related to the investigational product. This was diarrhea reported in the THS 2.2 Menthol arm during the Confinement Period and was considered not expected. In addition, 6 AEs were considered related to study procedures, with 4 AEs during the Confinement Period and 2 AEs during the Ambulatory Period.

Overall, the most frequent AEs reported post-randomization by SOC were Investigations, which were experienced by 24/78 subjects (30.8%) in the THS 2.2 Menthol arm, 8/42 subjects (19.0%) in the mCC arm, and 10/40 subjects (25.0%) in the SA arm.

The most frequent AEs by PT reported were decreased hemoglobin, decreased neutrophils, increased blood TGs, and nasopharyngitis, with the majority of incidences occurring for these PTs during the Ambulatory Period. Throughout the study, 11/78 subjects (14.1%) in the THS 2.2 Menthol arm, 3/42 subjects (7.1%) in the mCC arm, and 3/40 subjects (7.5%) in the SA arm experienced decreased hemoglobin (haemoglobin decreased). Overall the proportion of subjects who experienced neutrophil count decreased, blood TG increased, and nasopharyngitis was $\leq 5.0\%$ and the proportions of subjects in each study arm were similar.

Overall, 53 subjects in the THS 2.2 Menthol arm (67.9%) reported a total of 144 major device events or malfunctions; 26 subjects (33.3%) during the Confinement Period and 44 subjects (56.5%) during the Ambulatory Period. None of these events led to an AE.

There were no clinically significant or relevant abnormalities in vital signs, ECG, or spirometry findings.

CONCLUSIONS:

The study demonstrated that switching from mCC to THS 2.2 Menthol use in a Japanese smoking population resulted in substantial reductions in exposure to 15 HPHCs, with the majority of the reduction already achieved after 5 days in Confinement and sustained throughout the 85 days of the Ambulatory Period of the study. The kinetics of the reductions observed for the majority of BoExp in the THS 2.2 Menthol arm were close to that observed in the SA arm, in both the timing and magnitude of the reductions.

The exposure to nicotine in the THS 2.2 Menthol arm initially decreased at Day 1 compared to baseline and further increased from Day 1 to Day 5, reaching a steady state on Day 30. A similar trend was observed in the number of THS Menthol Tobacco Sticks used per day over time. The observed changes in the HST parameters, characterized by an increase in puff frequency and consequently the overall number of puffs over time, correlated well with the changes in product use and nicotine exposure.

While the level of nicotine exposure observed at Day 5 was higher for THS 2.2 Menthol compared to mCC users, the difference between the 2 reduced over time following an increase of daily mCC use during the Ambulatory Period, so that the exposure to nicotine reached a steady state at Day 30 in the THS 2.2 Menthol arm and a continuous increase in nicotine levels in the mCC arm over time. Comparable levels of nicotine exposure were achieved in both arms following 90 days of product use.

In conclusion, the observed kinetics of nicotine exposure, the number of THS Menthol Tobacco Sticks used over time, the observed changes in puffing topography parameters and the results of subjective effect measures showed comparable results for the THS 2.2 Menthol and the mCC arms from Day 30 onwards. These data suggested that subjects are able to quickly adapt to the THS 2.2 Menthol product, despite the



different characteristics respective to their own preferred brand of mCC, by titrating and controlling their desired level of nicotine exposure, and consequently achieving similar satisfaction with the use of THS 2.2 Menthol compared to mCC.

The directional shift of CREs in the THS 2.2 Menthol arm towards SA adds to the clinical relevance of the observed exposure reduction, and may indicate that the exposure reduction attained by switching to THS 2.2 Menthol may translate into biological and functional changes, potentially reducing the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.

There were no SAEs or severe AEs reported in this study and no randomized subjects were discontinued due to an AE. The incidence of subjects experiencing AEs during the study was low, with the majority of AEs mild in severity. The number of AEs and the percentage of subjects reporting AEs exhibited a similar incidence between all study arms.

Overall, the study results demonstrated a sustained exposure reduction to HPHCs after switching to THS 2.2 Menthol in both confined and ambulatory settings, close to levels observed after SA, transforming into favorable changes in CREs, while providing an acceptable alternative to users with regards to taste, ritual, sensorial experience, and nicotine delivery. Therefore, THS 2.2 Menthol might be a suitable substitute for mCC for adult smokers with the potential to reduce the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

1-NA	1-aminonaphthalene
1-OHP	1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
8-epi-PGF _{2α}	8-epi-prostaglandin F2 alpha
11-DTX-B2	11-dehydro-thromboxane B2
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical, Therapeutic, and Chemical
AUC _{0-24 h}	Area under the time-concentration curve from 0 to 24 hours
B[a]P	3-hydroxybenzo(a)pyrene
BoExp	Biomarker of exposure
BLOQ	Below the limit of quantification
BMI	Body mass index
CAF	Caffeine
C _{avg}	Weighted average concentration over 24 hours
CC	Conventional cigarette
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhemoglobin



C _{peak}	Peak plasma concentration
CRE	Risk marker, Clinical risk marker
CRF	Case report form
CRO	Contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variance
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
ECG	Electrocardiogram
FAS	Full Analysis Set
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 aminotransferase
GVP	Gas vapor phase
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High density lipoprotein
HEMA	2-hydroxyethyl mercapturic acid
HIV	Human immunodeficiency virus
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHC	Harmful and potentially harmful constituent
hs-CRP	High sensitive C-reactive protein



HST	Human smoking topography
ICF	Informed consent form
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IM	Investigator's meeting
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization of Standardization
LDL	Low density lipoprotein
LED	Light emitting device
LLOQ	Lower limit of quantification
LS	Least squares
mCC	Menthol conventional cigarette
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenyl mercapturic acid
mRNA	Messenger ribonucleic acid
miRNA	Micro ribonucleic acid
MNWS	Minnesota Nicotine Withdrawal Scale
MRTP	Modified risk tobacco product
NEQ	Nicotine equivalent
NNAL	4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosornicotine
NRT	Nicotine replacement therapy
NSAID	Non-steroidal anti-inflammatory drug
o-tol	o-toluidine



PAH	Polycyclic aromatic hydrocarbons
PK	Pharmacokinetic
PMI	Philip Morris International
PP	Per protocol
Pred	Predicted
PT	Preferred term
PX	Paraxanthine
QC	Quality control
QSU-brief	Questionnaire of Smoking Urges (brief version)
SA	Smoking abstinence
SAP	Statistical analysis plan
SAE	Serious adverse event
S-BMA	S-benzylmercapturic acid
SD	Standard deviation
SES	Socio-economic status
sICAM-1	Soluble intercellular adhesion molecule-1
SIV	Site Initiation Visit
SOC	System organ class
SOP	Standard Operating Procedure
TC	Total cholesterol
TFL	Tables, figures, and listings
TG	triglyceride
THS 2.2 Menthol	Tobacco Heating System 2.2 Menthol
t_{peak}	Time to peak concentration
TPM	Total particulate matter
ULOQ	Upper limit of quantification



VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	World Health Organization - Drug Dictionary Enhanced



4 DEFINITION OF TERMS

The following special terms are used in this report.

Baseline Period	06:30 AM on Day -1 until 06:29 AM of Day 1
Biomarker of exposure (BoExp)	An exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism.
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 was a convenient size to carry around, and could itself be recharged from a mains power source.
Day 30 Visit, Day 60 Visit, and Day 90 Visit	Day 30 Visit, Day 60 Visit, and Day 90 Visit started on Day 30, Day 60, and Day 90, respectively at approximately 08:00 AM (check-in of the subject on site) until the check-out of the day after respectively on Day 31, Day 61, and Discharge on Day 91. This was to allow 24-hour urine collection.
End of study	End of Study was defined as Discharge on Day 91 (Day 90 Visit) of the subject plus 28 days of safety follow-up.
Enrollment	On Day -2 for eligible subjects after all applicable inclusion and exclusion criteria had been satisfactorily met and the subject was willing and ready to use the THS 2.2 Menthol (the trial of THS 2.2 Menthol was the last assessment prior to enrollment).
Exposure Period in Confinement	06:30 AM of Day 1 until Discharge on Day 6.
Exposure Period in the Ambulatory Setting	From Discharge on Day 6 until Discharge on Day 90 11:00 PM.
Menthol conventional cigarette (mCC)	The term 'menthol conventional cigarette' refers to manufactured and commercially available menthol cigarettes and excluded hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.



Product use time periods	Period 1: ([Day 1-Day 6 Confinement]) Period 2: ([Day 6 Ambulatory-Day 30 Visit]) Period 3: ([Day 30 Visit-Day 60 Visit]) Period 4: ([Day 60 Visit-Day 90 Visit])
Randomization	Assignment of the subject randomization number in the Interactive Web and Voice Response System. This could have been done at any time on Day 0; however, subjects were not informed of their randomization group and number prior to Day 1.
Run-in Period	Admission to site until 06:29 AM of Day -1.
Safety Follow-up Period	After Discharge on the Day 91, a 28-day safety follow-up was done for the recording of spontaneously reported new adverse events (AEs)/serious AEs (SAEs) and the active follow-up of ongoing AEs/SAEs by the site. In general, any AE was followed-up until resolved, 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 informed consent form (ICF) signature to the time of enrollment were considered Screening failures and were replaced by other subjects.
THS Menthol Tobacco Stick	The THS 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.
THS Tobacco Stick Holder (Holder)	The function of the Holder (Model 4.2) is to heat the THS 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 THS Menthol Tobacco Stick).
Discharge	Discharge on Day 6: when the subject was released from the site (Confinement Period) after all the procedures on the Day of Discharge (Day 6) had been conducted prior to entering into the Ambulatory Period. Discharge on Day 91 (Day 90 Visit): when the subject was released from the site on Day 91 and entered the 28-day safety Follow-up Period.



Tobacco Heating Device	The Device comprises everything in THS 2.2 Menthol, except the THS Menthol Tobacco Stick.
Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)	THS 2.2 Menthol comprises the following components: THS Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains 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 (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), and 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 for the Final Protocol Version 1 on 18 July 2013. An amendment was incorporated into Version 2.0 of the protocol following the Sponsor's decision to terminate the study at the Seishukai Clinic following ICH/GCP non-compliance (see [Section 9.8.1](#)) and was granted IRB approval on 18 December 2013. The study continued at the Tokyo Heart Center. A further amendment was incorporated into Version 3.0 of the protocol to update changes to the name of a participating laboratory and to update the Sponsor's Medical Writer. The IRB approval notification was obtained at the IRB meeting held on 21 May 2014.

The written approvals from the IRB were filed in the Principal Investigator's files, and another copy was filed in the Study Master File. The study started after the Principal Investigators had obtained written confirmation of favorable opinion/approval from the concerned IRB.

A copy of the final protocol (Version 1.0 dated 26 June 2013), and the amended protocols (Version 2.0 dated 19 November 2013 and Version 3.0, dated 07 April 2014) are 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 (see [Section 9.6.4](#) for further details on ICH/GCP compliance in this study).

The Principal Investigators agreed to conduct the clinical study in compliance with the protocol agreed upon with the Sponsor and approved by the IRB. The Principal Investigators and the Sponsor signed the protocol (and protocol amendments) to confirm this agreement. A copy of the Declaration of Helsinki, 2008 [1] was placed in the Principal Investigator's Study File.

5.3 Subject Information and Consent

Before or at the Screening Visit, the Principal Investigator or designee ensured each subject was given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the Principal Investigator or the designee answered all questions the subject might have to his/her full satisfaction. The subject had sufficient time for consideration of his/her participation in the study and was notified that he/she was free to discontinue his/her participation at any time. Once the subject had received all necessary information, and if he/she agreed to participate, this was documented in the ICF by the date and signature of both the subject and the person who conducted the informed consent discussion. No study-specific procedures were performed before the ICF had been signed.

The original, dated and signed ICF(s) was kept in the Principal Investigator file at the site, and a copy was given to the subject.

The subject was informed that additional data analysis 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 fully covered by data confidentiality, as for the main analysis described in this protocol.

5.4 Sample Banking Informed Consent Form

Subjects were provided with information and were, on an ICF specific to transcriptomics bio-banking, asked for their consent to collect blood samples for bio-banking for transcriptomics (pharmacogenomics) in order to study the variation of the ribonucleic acid (messenger ribonucleic acid [mRNA] and micro ribonucleic acid [miRNA]) in smokers using THS 2.2 Menthol as compared to smokers continuing to smoke menthol conventional cigarettes (mCC), or smokers switching to smoking abstinence (SA). The comparison was based on previously described biological networks. In-house data from an exploratory study to assess the reduction of exposure to harmful and potentially



harmful constituents (HPHCs) (clinical trial dot.gov identifier: NCT01780714) in smokers switching to THS 2.1 as compared to smokers continuing to smoke conventional cigarettes (CC) showed that using THS 2.1, the earlier version of THS 2.2, resulted in significant variation of RNA characteristics as compared to smoking CC. A copy of the Subject Information and ICF Optional Transcriptomic Research Study (Version 1, dated 05 July 2013) is provided in [Appendix 16.1.3](#).

Subjects were also provided with separate subject information and ICF for samples (serum/plasma and urine) which were stored in a bio-bank for subsequent analysis of biomarkers of exposure (BoExp) and/or risk markers (CREs) following completion of this study. A copy of the Subject Information and ICF Optional Biomarker of Exposure/Risk Marker Research (Version 1, dated 05 July 2013) is provided in [Appendix 16.1.3](#).

Each subject was given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of bio-banking, and the Principal Investigator or designee was to answer all questions the subject had to his/her full satisfaction. The subject was notified that he/she was free to discontinue his/her participation at any time. Once the subject had received all necessary information, and if he/she agreed to participate, this was documented by the date and signatures of the subject, the Principal Investigator, and the person who conducted the informed consent discussion.

The subject's consent to storage of any samples in a bio-bank was not a requirement for study participation and the subject's participation in the study did not depend on them providing consent for sample bio-banking.



6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Principal Investigators, sites of study and responsible personnel are listed below.

Study Sites (Clinical Conduct)	Seishukai Clinic 3-18-5, Matsugaya, Taitou-ku Tokyo 111-0036, Japan Tokyo Heart Center Osaki Hospital 5-4-12, Kita-Shinagawa, Shinagawa-ku, Tokyo 141-0001, Japan
Principal Investigators	Mamoru Oki, MD, PhD (Seishukai Clinic) Professor Masahiro Endo, MD (Tokyo Heart Center)
Sponsor	Philip Morris Products S.A. PMI Research and Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Manager P1 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 (until 31 October 2014)
Biostatistician	Nicola Lama, PhD
Clinical Study Manager	Muriel Benzimra
Study Data Manager	Kishor Lad
Clinical Laboratory and Analytical Sites Clinical Safety Laboratory (Screening)	(b) (4)
Carboxyhemoglobin (COHb)	(b) (4)
General Manager Study Coordinator	(b) (4)



Clinical Safety Laboratory (Study duration not including Screening)	Covance Central Laboratory Services 7 Rue Moïse-Marcinhes, 1217 Meyrin/Geneva, Switzerland
Project manager	Nathalie Mathieux, PhD (Clinical safety Laboratory)
Plasma and Urine BoExp ¹ (Urine: 3-HPMA, Total NNN, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, B[a]P, HMPMA, Total NNAL, NEQ, 8-epi-PGF _{2α} , 11-DTX-B2; Plasma: nicotine and cotinine, caffeine and paraxanthine, cotinine and trans-3'-hydroxycotinine)	Celerion Inc. 621 Rose Street, Lincoln, Nebraska 68502, USA
¹ See Table 1 for definitions of BoExp	
Bioanalytical Principal Investigator Quality Assurance Manager	Kirk Newland, BSc Crystal Bickford, BA
Urine BoExp ¹ (Urine: Total 1-OHP, S-BMA, S-PMA, MHBMA ¹)	Celerion Switzerland AG Allmendstrasse 32 CH-8320 Fehraltorf (Zürich) Switzerland
¹ See Table 1 for definitions of BoExp	
Bioanalytical Principal Investigator Quality Assurance Manager	Markus Bachmann, PhD Diana Bürgin
Risk Markers (Urine: homocysteine, hs-CRP, HbA1c, LDL cholesterol, HDL cholesterol, and soluble intercellular adhesion molecule-1[sICAM-1])	Covance Japan Co. Ltd Kyobashi Yamamoto Bldg., 7F, 3-12-7, Kyobasi, Chuo-ku, Tokyo 104-0031, Japan
Senior Laboratory Director Manager, Laboratory Operations	Tufail Syed, MD Annabelle P. Robles



Risk Markers (Urine: Fibrinogen)	BML Covance CLS Clinical Trial Laboratory CB Lab 3611-1 Matoba Kawagoeshi Saitama 350-1101 Japan
Senior Laboratory Director Manager, Laboratory Operations	Tufail Syed, MD Annabelle P. Robles
Exploratory Markers: Urine Ames mutagenicity	Labstat International ULC 262 Manitou Drive, Kitchener ON, Canada N2C 1L3
Scientist	Amit Trivedi (Contributing Scientist and Technical Director, Biological Activity)
THS Filter Analysis	Labstat International ULC 262 Manitou Drive, Kitchener ON, Canada N2C 1L3
Technical Director	Pete Joza
Topography	Philip Morris International. Research and Development, Human Smoking Topography Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Senior Associate Scientist	Anthony Bruchet, Valerie Poux
Clinical Research Organization (Study Monitoring)	(b) (4)
Project Manager	(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)



	(b) (4)
Senior Project Manager	(b) (4)
Clinical Research Organization (Serious Adverse Event and Pregnancy Reporting)	(b) (4)
Safety Scientist	(b) (4)
Clinical Research Organization (Data Management and Study Reporting)	Covance Clinical Research Unit (CRU) Ltd. Springfield House, Hyde Street Leeds, LS2 9LH, UK
Project Manager	Jo Taylor, BSc, PhD Maidenhead, UK
Medical Director	Luke Chung, MD, MPH Singapore
Data Manager	Mary Russo Princeton, NJ, USA
Pharmacokineticist	Stuart Hossack, BSc Leeds, UK
Statistician	John Hunter, BSc, MSc Madison, WI, USA
Medical Writer	Louise Wakenshaw, BSc, PhD Leeds, UK
Clinical Research Organization (Statistical Analysis and Tables, Figures, and Listing Production)	(b) (4)

The Principal Investigators and other important participants and associated curricula vitae are provided in [Appendix 16.1.4](#).

The signatures of the Principal Investigators, 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]. To those smokers who are not able or not willing to quit, Philip Morris International (PMI) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases. These products are now referred by the US Food and Drug Administration (FDA) as modified risk tobacco products (MRTPs) [5]. The Institute of Medicine refers to smoking cessation as the “gold standard” for assessing risk reduction, and also that “the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit” [6].

More than 5,300 smoke constituents (the chemicals formed when tobacco is burned or combusted) have been identified, and more than 100 of them have been categorized as HPHCs. PMI's focus has been the development of products that replicate the “smoking experience” as much as possible by providing nicotine in a way that closely parallels mCC, but which limit pyrolysis and combustion by heating tobacco at significantly lower temperatures than is required for the combustion of mCC. This is likely to offer a more acceptable alternative to mCC for smokers because of the potential to reduce the levels of HPHCs.

The product developed by PMI, which 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 observed for the combustion CC, which can reach 900°C. The THS 2.2 Menthol is composed of the THS Tobacco Stick Holder', dedicated special THS Menthol Tobacco Sticks made of conventional tobacco, a Charger, and different accessories. The energy of the THS Tobacco Stick Holder is sufficient for approximately a 6-minute session. Unlike CC, the Menthol Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of THS 2.2 and its predecessors are described in the IB [7] and supported the initiation of the 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 were increased compared to the CC. The biological activity was tested in a number of *in vitro* assays to assess the cytotoxicity and the genotoxicity of the aerosol fractions, total particulate matter (TPM), and gas vapor phase (GVP). *In vitro* and *in vivo* results corroborated the concept that absence of combustion when consuming tobacco



substantially lowers toxic effects seen in these biological models. Further details are given in the IB [7].

Several clinical studies have been conducted on THS 1.0 and THS 1.0 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 smoking CC, both in controlled and ambulatory conditions. To date 3 clinical studies have been conducted with THS 2.2 Menthol. These studies have completed the clinical stage and are waiting reporting.

The previous version of THS 2.2 non-Menthol, namely THS 2.1, was tested in 2 exploratory clinical studies to measure the nicotine plasma kinetic profile (www.clinicaltrial.gov identifier: NCT01780688) and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1 (www.clinicaltrial.gov identifier: NCT01780714). The observed nicotine plasma kinetic profile for THS 2.1 was similar to CC, with significant reductions in the exposure to the majority of selected HPHCs [7]. Clinical studies conducted so far have revealed no safety concerns for any of the previous versions of THS 2.2 tested.

The overall goal of the study was to provide information on the reduction in the levels of selected BoExp to HPHCs and to obtain safety information in subjects using the THS 2.2 Menthol as compared to smokers continuing smoking their preferred brand of mCC in a confinement setting for 5 days followed by an ambulatory setting for 85 days. Smokers who were asked to abstain from using any nicotine/tobacco-containing products were used as a reference point. The smokers allocated to the THS 2.2 Menthol and mCC arms were allowed to use the product they were allocated to *ad libitum*.

An additional aim of the study was to understand the effect of using THS 2.2 Menthol on selected variables and their potential association to the reduced exposure to HPHCs (e.g., additional BoExp, cytochrome P450 1A2 [CYP1A2], and cytochrome P450 2A6 [CYP2A6] enzymatic activity, pharmacokinetic [PK] profile of nicotine and cotinine, product evaluation, product use and related subjective effects, human smoking topography [HST], and CREs).



8 STUDY OBJECTIVES

8.1 Primary Objectives and Endpoints

The primary objectives and endpoints of this study were:

1. To demonstrate the reduction of primary BoExp to HPHCs (except Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [NNAL]) in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints

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

Endpoints

- Total NNAL level (concentration adjusted for creatinine) in 24-hour urine fraction as measured on Day 90 Visit.

The BoExp for the primary objective are listed in [Table 1](#).

8.2 Secondary Objectives and Endpoints

The secondary objectives and endpoints of this study were:

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

Endpoint

- Number of mCC or THS Menthol Tobacco Sticks smoked daily as reported on the log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.
2. To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoint

- BoExp listed as secondary (expressed as quantity excreted or concentration adjusted for creatinine) (Table 1) as measured in 24-hour urine on Day 5 and Day 90 Visit.
3. To describe the levels of primary and secondary BoExp over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoint

- BoExp listed as primary and secondary (Table 1) from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit, and Day 90 Visit as follows:
 - Carbon monoxide ([CO] expressed as ppm) in exhaled breath.
 - COHb in blood (expressed as % saturation of hemoglobin).
 - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine.
4. To determine the levels of nicotine over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire Exposure Period.

Endpoints

- Nicotine equivalents (NEQ; expressed as quantity excreted and concentration adjusted for creatinine) (Table 1) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
 - Nicotine and cotinine in plasma from Day 1 to Day 4, Day 5, and on Day 30 Visit, Day 60 Visit, Day 90 Visit.
5. To describe the PK profiles of nicotine and cotinine in a confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints

- Peak (highest concentration along the day) on Day 5.
 - Time to peak (t_{peak} ; actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
 - Weighted average concentration over 24 hours on Day 5 (C_{avg}).
6. To describe the change in CYP1A2 enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.

Endpoint

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



7. To monitor the safety profiles during the study.

Endpoints

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

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

Endpoints

- Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
- Soluble intercellular adhesion molecule-1 in serum on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- White blood cell (WBC) and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-prostaglandin F2 alpha (8-epi-PGF_{2α}) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
- Body weight and waist circumference on Day 90 Visit.

Table 1 Primary and Secondary Biomarkers of Exposure and Biomarkers of Exposure to Nicotine

	Biomarkers of Exposure (BoExp)	HPHCs	Matrix
Primary BoExp (Day 5)	Monohydroxybutenyl mercapturic acid (MHBMA)	1,3-butadiene	Urine
	3-hydroxypropylmercapturic acid (3-HPMA)	acrolein	Urine
	S-phenylmercapturic acid (S-PMA)	benzene	Urine
	Carboxyhemoglobin (COHb)	carbon monoxide (CO)	Blood



Primary BoExp (Day 90 Visit)	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)	4 (methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK)	Urine
	Carbon monoxide	CO	Exhaled breath
Secondary BoExp	Total 1-hydroxypyrene (1-OHP)	pyrene	Urine
	Total N-nitrosornicotine (NNN)	N-nitrosornicotine	Urine
	4-aminobiphenyl (4-ABP)	4-aminobiphenyl	Urine
	1-aminonaphthalene (1-NA)	1-aminonaphthalene	Urine
	2-aminonaphthalene (2-NA)	2-aminonaphthalene	Urine
	o-toluidine (o-tol)	o-toluidine	Urine
	2-cyanoethylmercapturic acid (CEMA)	acrylonitrile	Urine
	2-hydroxyethyl mercapturic acid (HEMA)	ethylene oxide	Urine
	3-hydroxybenzo(a)pyrene (B[a]P)	benzo(a)pyrene	Urine
	3-hydroxy-1-methylpropylmercapturic acid (HMPMA)	crotonaldehyde	Urine
	S-benzylmercapturic acid (S-BMA)	toluene	Urine
	Nicotine equivalents (NEQ): free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide	nicotine	Urine
BoExp to nicotine	Nicotine	nicotine	Plasma
	Cotinine	nicotine	Plasma

8.3 Exploratory Objectives and Endpoints

The exploratory objectives and endpoints of this study were:

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

Endpoints

- Excretion of mutagenic material in urine: Ames mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24-hour urine.
- Subjective effect of smoking: Questionnaire of Smoking Urges (brief version) (QSU-brief); questionnaire Minnesota Nicotine Withdrawal Scale (MNWS) – Revised on Day 5, and Day 90 Visit.
- Cytochrome P450 2A6 activity: in plasma on Day 6, and Day 90 Visit using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.



- Nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire: score from FTND questionnaire on Day 90 Visit.
- 2. To evaluate in smokers switching from mCC to THS 2.2 Menthol and smokers continuing smoking mCC the relationship between NEQ and:

Endpoints

- The BoExp of the primary and secondary objective on Day 5 and on Day 90 Visit in 24-hour urine.
- Selected risk markers (CREs; hs-CRP, homocysteine, blood glucose, LDL cholesterol, HDL cholesterol, TG, TC, fibrinogen, HbA1c, sICAM-1, WBC, platelet count, 8-epi-PGF_{2α}, 11-DTX-B2) in respective body matrix when available on Day 5 and Day 90 Visit.
- 3. To describe the following parameters over the course of the study in smokers switching from mCC to the THS 2.2 Menthol as compared to smokers continuing smoking mCC:

Endpoints

- Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
- Smoking pattern: HST parameters and HST questionnaire.
- 4. To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol:

Endpoints

- Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
- Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm (during the Confinement Setting only).
- 5. To describe the product use over the course of the study according to the product preference of the subject:

Endpoint

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

8.4 Study Hypotheses and Evaluation Criteria

8.4.1 Hypotheses

The hypothesis tested was that the geometric mean level of the BoExp for THS 2.2 Menthol were lower relative to mCC. For BoExp included as endpoints in the primary



objective, the hypothesis was tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and on Day 90 Visit for Total NNAL. The secondary objectives tested the BoExp included as endpoints in the primary objective and the remaining BoExp. If the hypothesis test was significant at Day 5 then the endpoint was further tested Day 90.

8.4.2 Evaluation Criteria

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



9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a randomized, controlled, open-label, 3-arm parallel group, multi-center study design with a stratified randomization by sex and daily average cigarette consumption over the last 4 weeks as reported during the Screening Visit (smokers smoking 10-19 mCC and smokers smoking >19 mCC per day) (Figure 1).

This was an *ad libitum* smoking study without limitation of the maximum number of mCC/THS Menthol Tobacco Stick use.

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

Screening Period:

The Screening Period covered 4 weeks (Day -30 to Day -3) prior to Admission to the clinic (Day -2) (Figure 1). A demonstration of the THS 2.2 Menthol product was given by the study collaborator during the Screening Visit. Subjects returned to the site and were in a confined setting for 9 days from Day -2 onwards.

Run-in period:

The Run-in Period was defined as from Admission on Day -2 until 06:29 AM of Day -1. Prior to enrollment on Day -2, as the last procedure of the eligibility assessments, subjects performed a product test of the THS 2.2 Menthol (using up to 3 THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product test was performed only after pregnancy was excluded by a negative urine pregnancy test. Enrollment took place after all inclusion and exclusion criteria had been satisfactorily met. Only subjects willing and able to use the product were enrolled.

All subjects participating in the product trial on Day -2 who were not enrolled into the study entered a 28 day safety Follow-up Period.

Baseline Period:

The Baseline Period was defined as from 6:30 AM on Day -1 until 6:29 AM on Day 1. All subjects continued smoking their single preferred brand of mCC and baseline values were recorded. On Day 0, subjects were randomized to one of the 3 study arms in a 2:1:1 ratio using a stratified randomization (Table 2).

**Table 2 Definition of Study Arms**

Study arm	Number of subjects planned
THS 2.2 Menthol <i>ad libitum</i>	80
mCC <i>ad libitum</i>	40
SA	40

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

Subjects were informed of their randomized study arm by the study collaborators on Day 1 prior to 06:30 AM.

Exposure Period:

The Exposure Period was defined as from Day 1, 06:30 AM until 11:00 PM on Day 90 and Day of Discharge was defined as Day 90, 11:00 PM until Discharge on Day 91. The Exposure Period included both the Exposure Period in Confinement and the Exposure Period in the Ambulatory Setting.

Product use time periods:

Within the Exposure Period, 4 periods were defined as the following: Period 1, Day 1 to Day 6 Confinement; Period 2, Day 6 Ambulatory to Day 30 Visit; Period 3, Day 30 Visit to Day 60 Visit; and Period 4, Day 60 Visit to Day 90 Visit.

Exposure Period in Confinement:

The Exposure Period in the Confinement Period was defined as from Day 1, 06:30 AM until Discharge on Day 6 consisting of 5 days of *ad libitum* use of the assigned product between 06:30 AM and 11:00 PM in THS 2.2 Menthol and mCC arms. Subjects allocated to the SA arm were asked to abstain from smoking and were not provided with medication to support SA. Subjects were provided with psychological support during the period of SA. Use of any tobacco/nicotine containing product other than the assigned product/regimen was forbidden and may have, at the discretion of the Principal Investigator, resulted in subject withdrawal.

Twenty-four-hour urine was collected from Day -1 to Day 5 on site. The end of the 24-hour urine collection for Day 5 ended in the morning of Day 6 prior to Discharge.

On Day 6, the safety procedures were conducted before discharge from the clinic after 9 days in a confined setting. Use of products was allowed on Day 6 in the THS 2.2 Menthol and mCC arms according to product arm allocation, but only after CYP2A6 activity measurements, cough and MNWS questionnaires, and spirometry had been performed.

Exposure Period in Ambulatory Setting:

The Exposure Period in the Ambulatory Setting was defined as from Discharge on Day 6 until 11:00 PM on Day 90 and Day of Discharge was defined as from 11:01 PM on Day 90 until Discharge on Day 91.

After Discharge on Day 6, subjects were instructed to continue their assigned product/regimen in an ambulatory setting for 85 days. Subjects were allowed to use nicotine replacement therapy (NRT) if considered necessary by the Principal Investigator or requested by the subject.

Subjects were required to make 3 Ambulatory Visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each visit covered 2 consecutive days on site. For the Day 30 Visit, the subject checked in at approximately 08:00 AM on Day 30, and checked-out on Day 31. For the Day 60 Visit, the subject checked in at approximately 08:00 AM on Day 60, and checked-out on Day 61. For the Day 90 Visit, the subject checked in at approximately 08:00 AM on Day 90, and was discharged on Day 91 after all the safety examination procedures had been performed.

At each Ambulatory Visit (Day 30 Visit, Day 60 Visit, and Day 90 Visit) 24-hour urine was collected at the site. The end of the 24-hour urine collection for the Day 90 Visit ended in the morning of Day 91 at 09:00 AM.

On Day 30, Day 60, and Day 90, subjects in the THS 2.2 Menthol and mCC arms were allowed to use their assigned product from approximately 08:00 AM to 11:00 PM. Smoking/product use before 08:00 AM on Day 30, Day 60, and Day 90 was unrestricted. On Day 31 and Day 61, product use was allowed from 06:30 AM. The end of the Exposure Period was fixed at 11:00 PM on Day 90.

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

At the Day of Discharge of the Day 90 Visit, subjects were discharged from the investigational site after all safety examination procedures had been conducted. Subjects who were discontinued from the study underwent the Day of Discharge procedures as soon as possible and entered the period of safety follow-up.

During the Confinement and ambulatory settings, subjects in the SA arm were provided with support including psychological support as requested by the subject or considered necessary by the Principal Investigator/study collaborator.

Safety Follow-up Period:

After Discharge on Day 91, (or following product trial for subjects not enrolled into the study), subjects entered a 28-day safety Follow-up Period during which the recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs was performed by the study site. In general, all AEs were to be followed-up until

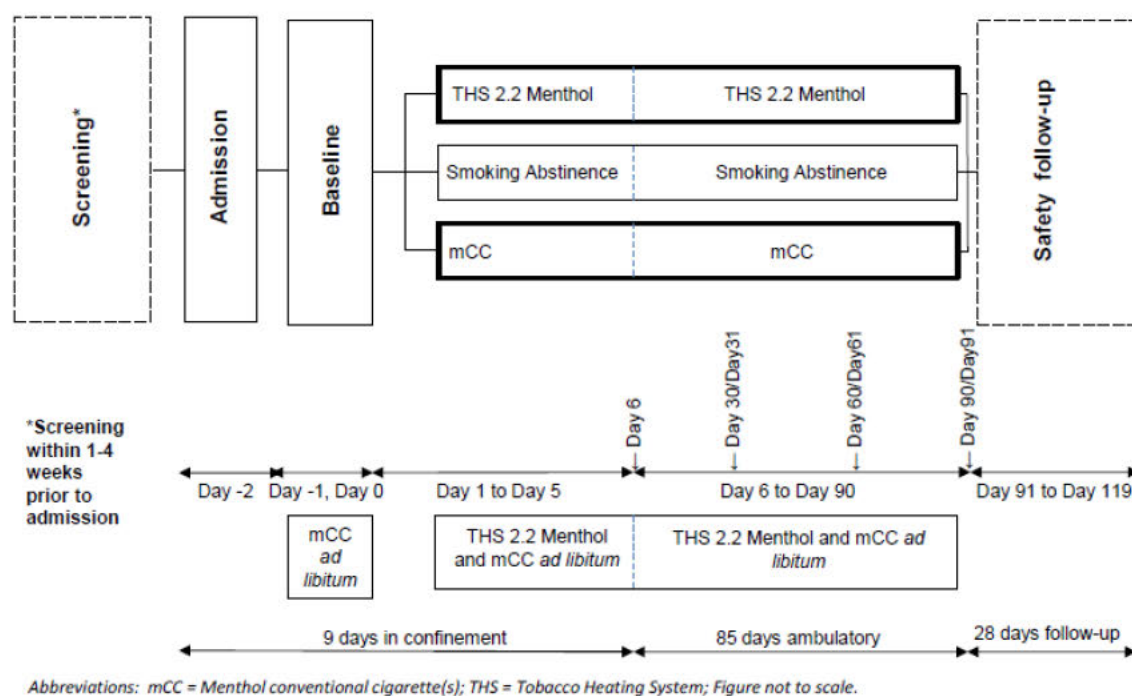


resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event had been found. The end of the study was defined as Discharge on Day 91 plus 28-day follow-up.

Subjects were not discontinued from the study for the use of nicotine/tobacco-containing products other than the assigned product/regimen. Subjects recorded in a product use electronic diary any use of CC (menthol or non-menthol), NRT, or other nicotine/tobacco-containing products.

During the study, any subjects who wanted to quit smoking were encouraged to do so, were referred to medical services, and discontinued from the study. This was applicable for all subjects during Screening to the Baseline Period and for subjects allocated to THS 2.2 Menthol or mCC arms during the Exposure Period.

Figure 1 Study Flow Chart



The detailed study protocol and a 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 aim of this study was to demonstrate reductions in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2 Menthol, a candidate MRTP, as compared to using mCCs.

The choice of HPHCs assessed in this study was derived from the World Health Organization (WHO) [8] and the draft guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke [9].

In the WHO list, 9 HPHCs (acrolein, CO, 1-3 butadiene, benzene, NNN, NNK, acetaldehyde, benzo[a]pyrene, and formaldehyde) with evidence of carcinogenicity, respiratory, and cardiac toxicity were recommended to be measured as priority in the smoke chemistry for mandated lowering [8]. In addition to the 9 HPHCs recommended to be measured by the WHO list, the FDA required that an additional 9 HPHCs are added for reporting (18 HPHCs in total in cigarette smoke) [9].

When selecting the HPHCs measured in this study, the following criteria were also considered:

- They are specific to the source of exposure with other sources being minor or non-existent.
- They are easily detectable using reliable, reproducible, and precise analytical methods.
- They ensure assessment of both gas and particulate phase of the THS 2.2 aerosol.
- They include a broad variety of chemical classes and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, and addiction potential).

Exposure to 4 HPHCs (acrolein, CO, 1,3-butadiene, and benzene) among the 9 priority HPHCs were assessed as the primary endpoints following 5 days of exclusive use of THS 2.2 Menthol, mCC, or SA because:

- They were decreased in smokers who switched to another candidate MRTP tested in exploratory studies for 5 days, similar to that observed in smokers who stopped smoking (data on file from previous study, [10]).
- They exhibit, on average, an elimination half-life of ≤ 24 hours. Therefore, the 5 days of exposure was deemed sufficient to reach the steady state within the THS 2.2 Menthol and SA arms (4 to 5 times the half-life was expected to lead to less than 5% of the original exposure levels of assessed biomarkers on Day 5).



- These HPHCs are several-fold higher in smokers than in smokers abstinent from smoking [11].

From the WHO and FDA lists, exposure to an additional 9 HPHCs (acrylonitrile, 4-ABP, 1-NA, 2-NA, benzo[a]pyrene, crotonaldehyde, NNK, NNN, and toluene) were assessed as secondary endpoints.

Total NNAL was selected as a primary endpoint after 90 days of THS 2.2 Menthol use as:

- This biomarker is tobacco specific [12], and exhibits, on average, an elimination half-life of 10 to 15 days. Therefore, the 90 days of exposure were deemed sufficient to reach the steady state with the THS 2.2 Menthol and SA arms (4 to 5 times the half-life was expected to lead to less than 5% of the original exposure levels at the Day 90 Visit).
- It was decreased in smokers who switched to another candidate MRTP after 5 days, (data on file from the previous study, [10]).

The HPHCs assessed in this study include 14 of the 18 HPHCs (except acetaldehyde, ammonia, formaldehyde, and isoprene), which are requested to be reported to the FDA [9]. Seven of the 9 toxicants (1,3-butadiene, acrolein, benzene, benzo[a]pyrene, CO, NNK, and NNN) are recommended for mandated lowering in mainstream cigarette smoke according to WHO [8].

In addition, some CREs were selected in order to evaluate biological changes in the THS 2.2 Menthol arm compared to the mCC arm using the SA arm as a reference point to verify if the trend of changes upon THS 2.2 Menthol use followed the same trajectory as SA. Among the ones selected, some well-known to be affected by smoking and to be reversible upon SA, were measured in this study as follows:

- Cytochrome P450 1A2 activity, the enzyme which mainly metabolizes nicotine, is decreased as soon as 5 days of SA and after 5 days of use of another candidate MRTP ([13] and data on file from a previous study [10]).
- Platelet function, assessed by measuring 11-DTX-B2 (a major stable metabolite of thromboxane A2 that mainly elicits mainly platelet aggregation). This marker was decreased after 1 week of SA [14] and after 5 days of use of another candidate MRTP [10].
- Blood pressure, hs-CRP, fibrinogen, homocysteine, fasting blood glucose, LDL cholesterol, HDL cholesterol, TGs, TC, HbA1c, waist circumference, sICAM-1, WBC, and 8-epi-PGF_{2α} were evaluated as additional CREs [15, 16] for cardiovascular monitoring purposes. According to the literature, some of these CREs are known to be sensitive to smoking cessation: the levels of HDL increase when the levels of sICAM-



1, WBC, and 8-epi-PGF_{2α} decrease following 1 to 3 months of smoking cessation [15, 17, 18].

- Body weight, as a mean increase of 4.5 kg in body weight is observed after 12 months of SA with the most weight gain occurring within the first 3 months of quitting [19].

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

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

The main reference in this study was smokers who continued to smoke mCC. Smokers who refrained from smoking (the SA arm) were used as a reference point for the maximum possible reduction in exposure to HPHCs (if they were fully compliant).

Subjects were randomized to 1 of the 3 study arms in a 2:1:1 ratio (THS 2.2 Menthol : mCC : SA). In each arm, a quota was applied for each sex and each of the smoking strata to ensure they represented at least 40% of the total randomized population.

A 2:1:1 randomization scheme was chosen to increase the power of the comparison of the arms versus THS and increase the number of subjects exposed to THS 2.2 Menthol in the Safety Population.

In this study, 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 [20].

The Confinement Period provided information on maximum possible exposure reductions in a well-controlled environment and allowed full control of daily cigarette consumption, whereas the Ambulatory Period provided a perspective of product usage in the real world setting where smoking of a few CC (menthol and non-menthol) in addition to THS 2.2 Menthol and SA was expected. It provided information on reduction in selected BoExp and related changes in selected CREs when THS 2.2 Menthol was used in a real world setting.

All subjects were asked to provide their own mCC according to their anticipated needs for the whole Confinement Period. This was to minimize any changes in their smoking behavior due to participation in the study.

9.3 Selection of 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. Smoking, healthy subject as judged by the Principal Investigator based on all available assessments from 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 spirometry, post-bronchodilator FEV₁ >80% predicted [21] value, and post-bronchodilator FVC >80% pred value], vital signs, physical examination, electrocardiogram (ECG), chest X-ray and medical history).
5. Subject smoked at least 10 commercially available mCCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine International Organization of 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).
6. The subject did not plan to quit smoking in the next 3 months.
7. The subject was ready to accept interruptions of smoking for up to 90 days.
8. The subject was ready to accept using the THS 2.2 Menthol.

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 requiring smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Principal Investigator.
4. The subject had a body mass index (BMI) <18.5 or ≥ 32 kg/m².
5. As per Principal Investigator judgment, the subject had medical conditions which required, or would have required in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may 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) within 14 days or within five half-lives of the drug (whichever was longer) prior to the Admission Day (Day -2), which had an impact on CYP1A2 or CYP2A6 activity.
8. If a subject had received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -2), it was decided at the discretion of the Principal Investigator if these could potentially interfere with the study objectives or subject's safety.
9. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid.
10. The subject had a positive alcohol test and/or the subject had a history of alcohol abuse that could have interfered with the subject's participation in the study.
11. The subject had a positive urine drug test.
12. Positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B, or hepatitis C virus (HCV).
13. Donation or receipt of whole blood or blood products within 3 months prior to Admission.
14. The subject was a current or former employee of the tobacco industry, or of their first-degree relatives (parent, sibling, or child).
15. 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, or child).
16. The subject had participated in a clinical study within 3 months prior to the Screening Visit.
17. 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:

18. Subject was pregnant (did not have negative pregnancy tests at Screening and at Admission) or was breast feeding.
19. Subject did not agree to use an acceptable method of effective contraception.*

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



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. This was fully documented in the source document and captured in the CRF.

When a subject had withdrawn or was removed from the study, the whole safety examination procedure planned on Day 6 was performed as soon as possible after the time of discontinuation unless the subject had withdrawn their informed consent to do so. After the time of discontinuation, the subject was entered into the 28-day period of safety follow-up. Subjects withdrawn or removed from the study could not re-enter the study.

Subjects could have been discontinued from the study for any of the following reasons:

- 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 not to be performed after diagnosis of pregnancy).
- The Sponsor or Principal Investigators terminated the study.
- Withdrawal was considered to be in the best interest of the subject or the other subjects.
- The subject wished to quit smoking.

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 have been discussed with the Contract Research Organization [CRO] 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 Principal Investigator to decide whether or not to withdraw the subject from the study.
- Non-compliance with the study procedures.

Smoking of CC (menthol and non-menthol) in the THS 2.2 Menthol or SA arms during the Ambulatory Period was not considered a reason for discontinuation of the subject from the study. However, the smoking of CCs (menthol and non-menthol) or use of any nicotine/tobacco-containing products including NRT other than the product/regimen the subject was assigned to during the Ambulatory Period was documented in the daily product use electronic diary.



Subjects discontinued 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 did not meet the entry criteria at Admission Day (Day -2) were considered a Screening failure until the time of enrollment and were replaced by other subjects.

Subjects who violated the entry criteria prior to enrollment, but who were considered eligible, were immediately discontinued from the study when the violation was detected. If subjects were not yet randomized, they could have been replaced.

9.3.3.2 Other Reasons for Removal of Subjects from Study

No other reasons were specified in the protocol for removal of subjects from the study.

However, as described in [Section 9.8.1](#), subjects were discontinued after the termination of a study site.

9.4 Investigational Products

9.4.1 THS 2.2 Menthol Product

THS 2.2 Menthol product was provided by the Sponsor and comprised the following components: THS Menthol Tobacco Stick, Holder, Charger, cleaning tool, a mains power supply, and a USB cable:

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 was a convenient size to carry around, and could be recharged from a mains power source.
Tobacco Stick Holder (Holder):	The function of the Holder (Model 4.2) was to heat the THS Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating was powered from an internal battery which delivered power for about 6 minutes (allowing complete use of a single THS Menthol Tobacco Stick).
THS Menthol Tobacco Stick (Menthol Tobacco Sticks):	The THS 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 product design was to provide an acceptable experience in which the HPHC levels in the aerosol were substantially reduced in comparison with mCC.

Pack batch number of packed THS Menthol Tobacco Sticks: B-05775. Production date: 12-Jun-2013. Expiry date: 11-Mar-2014 and B-08544. Production date: 25-Oct-2013. Expiry date: 24-Jul-2014 Device inventory data are listed in [Appendix 15, Listing 15.3.2.2](#).

9.4.2 Reference Product/Baseline Period Products

During the Run-in Period (Admission to clinic until 06:29 AM of Day -1) and the Baseline Period (from 06:30 AM of Day -1 until 06:29 AM of Day 1), all subjects continued smoking their preferred commercially available single brand of mCC. The mCC were not provided by the Sponsor. Users of hand-rolled cigarettes were not allowed to participate in the study.

The reference product to the THS 2.2 Menthol during the randomized Exposure Period was the subject's own preferred commercially available single brand of mCC.

All eligible subjects were asked to purchase their own preferred single brand of mCC prior to Admission and provide his/her anticipated amount of mCC for a total of 9 days plus 4 extra packs on Day -2 (Admission Day) to the site study collaborator.

During the Ambulatory Period, for the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, the subjects were asked to provide his/her anticipated amount of mCC, plus 2 extra packs.

9.4.3 Packaging and Labeling

At Admission, all study subjects provided their anticipated amount of mCC in sealed packs to the study site collaborator. The mCC packs provided by the subjects were not to have been opened and the cellophane wrapper was to be intact.

Each pack of mCC provided by the subject were labeled to identify which subject the cigarettes belonged to (labels were affixed by the study site collaborator to the cellophane wrapper of the lower part of the pack). Each pack of mCCs was labeled to identify necessary information to match the subject with their suppliers.

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



9.4.4 Storage and Accountability

The site study collaborator (the investigational product [IP] storage manager) designated by the head of the investigational site was responsible for the storage and accountability of the IPs in accordance with Sponsor requirements.

The THS 2.2 Menthol and mCC were stored in a secured storage site with access limited to authorized personnel only. Full accountability of the distributed products was ensured by a designated IP storage manager.

9.4.4.1 Confinement Period

On each day of the Confinement Period, study collaborators recorded on the accountability log every occasion from Day -1 to Discharge on Day 6 that mCCs were dispensed to a subject by the study collaborator and every occasion from Day 1 to Discharge on Day 6 that the THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, Charger, THS accessories) and THS Menthol Tobacco Sticks were dispensed to a subject.

Subjects returned each butt of mCC immediately after use from Day -1 to Day 6 for accountability. This was documented in an appropriate log.

Immediately after use, all tobacco plugs of all used THS Menthol Tobacco Sticks were separated from the filters and the tobacco plugs and the filters were collected from Day 1 to Day 5, using dedicated vials for accountability and subsequent analysis of potential combustion occurrences and nicotine retained in the filters. This was also documented in an appropriate log.

9.4.4.2 Ambulatory Period

Subjects in the THS 2.2 Menthol arm were to return any empty packs and partially used packs of THS Menthol Tobacco Sticks they used during the preceding weeks to the site for accountability. After accountability they were destroyed at study completion in accordance with Sponsor requirements.

All tobacco plugs from THS Menthol Tobacco Sticks used after check-in to the investigational site until 11:00 PM on Day 30, Day 60, and Day 90 were collected in dedicated vials for subsequent analysis of potential combustion occurrences. No filter analysis of the THS Menthol Tobacco Sticks was conducted during the visits of the Ambulatory Period.

No IP accountability was performed for subjects in the mCC arm or the SA arm.



9.4.5 Investigational Product Retention

Upon study completion all unused THS Menthol Tobacco Sticks were returned to the Sponsor and destroyed. All components of the THS 2.2 Menthol devices were returned to the Sponsor upon study completion.

Irrespective of the study arm, at Discharge from the clinic, the study collaborators returned to the subjects any remaining mCCs given to them on the day of Admission.

9.4.6 Method of Assigning Subjects to Study Arms

When all the eligibility criteria were met, randomization was performed through the Interactive Web and Voice Response System on Day 0 at any time during the day. Subjects were informed of their randomized study arm in the morning of Day 1, prior to 06:30 AM.

Subjects were randomized to 1 of the 3 study arms: THS 2.2 Menthol : mCC: SA in a 2:1:1 ratio. Stratified randomization was conducted by sex and by daily average cigarette consumption in the 4 weeks prior to the Screening Visit (those smoking 10 to 19 mCC and those smoking >19 mCC per day) reported by the subject. In each arm, each sex, and each of the smoking strata had a quota applied to ensure they represented at least 40% of the total randomized population.

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

The randomization scheme was generated by the statistical division within (b) (4) and none of the Study team (Sponsor, Covance, or (b) (4) Investigators, or study subjects had access to the randomization schema prior to randomization. The randomization scheme and codes are provided in [Appendix 16.1.6](#).

9.4.7 Administration of Investigational Products

Subjects were never requested or forced to smoke and were free to stop smoking at any time during the study. The study was designed as an *ad libitum* use study. During the Screening Period, subjects were allowed to smoke according to their smoking habits except during the procedures of the Screening Visit at the discretion of the site.

During the Confinement Period, product (mCC or THS 2.2 Menthol) use was generally allowed between 06:30 AM to 11:00 PM.



During the Ambulatory Period, there was no smoking/product restriction except at the Day 30 Visit, Day 60 Visit, and Day 90 Visit. On Day 30, Day 60, and Day 90, product use was allowed from 08:00 AM to 11:00 PM and during the Visit. Smoking/product use before 08:00 AM on Day 30, Day 60, and Day 90 was not restricted. On Day 31 and Day 61, product use was allowed from 06:30 AM. In the morning of Day 91, after the end of exposure in the Ambulatory Period (11:00 PM on Day 90), subjects were not allowed to smoke CC until CYP2A6 activity measurements, cough and MNWS questionnaires, and spirometry had been completed on site. The use of THS 2.2 Menthol was strictly forbidden for subjects in the mCC or SA arms.

9.4.7.1 Run-in Period

Smoking *ad libitum* was allowed prior to Admission and throughout the day except during the procedures. All subjects were allowed to continue smoking their single preferred brand of usual mCC *ad libitum*. All subjects underwent a THS 2.2 Menthol product test prior to enrollment.

Following the confirmation that the subject was able and willing to use the THS 2.2 product and willing to accept a period of SA, subjects were enrolled in the study.

9.4.7.2 Baseline Period

During the Baseline Period, all subjects were allowed to continue smoking their single preferred usual brand of mCC *ad libitum*.

9.4.7.3 Exposure Period

During the Confinement Period until Discharge on Day 6, subjects were not allowed to use any nicotine/tobacco-containing products other than their assigned product/regimen. On Day 6, when the safety procedures of Discharge were conducted, the use of product (THS 2.2 Menthol or mCC) was allowed but only after CYP2A6 activity measurements, cough and MNWS questionnaires, and spirometry were complete. Smoking was not allowed in the SA arm.

During the Ambulatory Period, subjects were instructed to continue exclusively using their assigned product/regimen. In the morning of Day 91, smoking was not allowed until CYP2A6 activity measurements, cough, and MNWS questionnaires, and spirometry had been conducted at the clinic.

9.4.7.3.1 THS 2.2 Menthol Arm

During the Exposure Period in Confinement, subjects randomized to the THS 2.2 Menthol arm exclusively used THS 2.2 Menthol from Day 1, 06:30 AM onwards until Discharge on Day 6. At Discharge on Day 6 and on each Ambulatory Visit, subjects were



instructed to continue exclusively using THS 2.2 Menthol *ad libitum* until 11:00 PM on Day 90.

9.4.7.3.2 mCC Arm

During the Exposure Period in Confinement, subjects randomized to the mCC arm continued smoking their mCC from Day 1, 06:30 AM onwards until Discharge on Day 6. At Discharge on Day 6, subjects were informed that they could continue to smoke their mCC *ad libitum* if they wished until 11:00 PM on Day 90.

9.4.7.3.3 SA Arm

During the Exposure Period in Confinement, subjects randomized to the SA arm were instructed to abstain from smoking from Day 1, 06:30 AM onwards until Discharge on Day 6. They were not provided with medication supportive for SA. On Day 6, on each Ambulatory Visit, and at any appropriate occasion, subjects in the SA arm were instructed to remain abstinent with or without NRT until Discharge of Day 91.

9.4.7.3.4 Safety Follow-up Period

During the safety Follow-up Period (after Discharge on Day 91 until Day 119), subjects in the THS 2.2 Menthol and mCC arms were free to smoke their own mCC *ad libitum*. Subjects in the SA arm who wished to continue their SA, were referred for further treatment as per the standard of care in the country in which the study was conducted, if requested by the subject. If subjects in the SA arm were unable to refrain from smoking, they were permitted to start smoking their own brand of mCC after Discharge on Day 91.

9.4.8 Smoking Stopping Rules for Smokers

For safety purposes, smoking 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 reasons at the discretion of the Principal Investigator.

9.4.9 Selection and Timing of Investigational Product Use for Each Subject

During the Confinement Period subjects did not have free access to their mCC or THS 2.2 Menthol (including the THS Menthol Tobacco Sticks). Both products were stored as described in [Section 9.4.4](#).

From Day -2 onwards during the Confinement Period, each mCC was dispensed to the subjects one by one. Subjects in the THS 2.2 Menthol arm were provided with THS Menthol Tobacco Sticks by the site study collaborators from Day 1 to Day 5, stick by stick. One mCC/THS Menthol Tobacco Stick was allowed at a time and documented in an appropriate log.



On each day of the Confinement Period, the time of dispense and return for each product was documented from Day-1 for mCC and from Day 1 for THS Menthol Tobacco Sticks onwards. The start of product use corresponded to the time of dispense of the first mCC/Menthol Tobacco Stick. The product was not promoted for commercial distribution or test market.

During the Ambulatory Period, subjects in the THS 2.2 Menthol arm were provided with an anticipated amount of THS Menthol Tobacco Sticks to cover the period until the next study visit. An additional number of THS Menthol Tobacco Sticks were dispensed to the subjects at these visits to cover for any unexpected delay to the visit schedule made by the subject. Extra deliveries of THS Menthol Tobacco Sticks in between 2 visits was arranged if requested. Subjects in the mCC arm bought their mCCs directly from shops.

The timing of THS 2.2 Menthol or mCC use was as described in [Section 9.4.7](#).

9.4.10 Blinding/ Unblinding

This was an open-label study; therefore, the subjects and Principal Investigators were unblinded to the subject's product assignment after randomization. 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 randomized product 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 study data managers	After the finalization of PMI blind database review.
PMI safety and clinical scientists	After the finalization of PMI blind database review.

As part of the PMI Quality Control (QC) activity, data were reviewed by Covance and PMI before database lock, with no access to the randomization scheme information. Full details including the definition of the blinded and unblinded PMI study teams are available in the data review plan (Version 2.0 dated 06 October 2014).

9.4.11 Prior and Concomitant Therapy

No medications were to be taken during the study from the Screening to Discharge on Day 91 without first informing the Principal Investigator. However, the Principal Investigator was responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescribing of medication was made in the best interests of the subject.



Concomitant medication use was first assessed at the Screening Visit. To be eligible for the study, any medication that impacted CYP1A2 and CYP2A6 metabolism was discontinued at least 2 weeks prior to Admission to the clinic or for at least 5 half-lives (whichever was longer). They were not to be used during the study until after Discharge on Day 91 (completion of the study), but were allowed during the safety follow-up.

During the Ambulatory Period, subjects in the SA arm were permitted to use NRT as judged by the Principal Investigator or if requested by the subject. No medication supportive for smoking cessation other than NRT was allowed in the study.

Concomitant use of NSAIDs and acetylsalicylic acid (including over-the-counter products) was not allowed, as all of them could have interfered with CREs such as 11-DTX-B2. Paracetamol was allowed at a daily total dose of up to 1500 mg. Any medication with an impact on the CYP1A2 and CYP2A6 metabolism (as prescription and over-the-counter products) as shown in [Table 4](#) and [Table 5](#) was to be avoided.

If the use of a concomitant medication could not be avoided for the subject's safety, it was fully documented in the source document and transcribed into the CRF. The drugs and substances listed in [Table 4](#) and [Table 5](#) are a selection of drugs considered to have an impact on CYP1A2 and/or CYP2A6 activity [22] (Drug Information Handbook, 2014). Prior to database close, concomitant medications were assessed according to their potential impact on CYP1A2 and CYP2A6 activity and on the study results. Analysis of the effects of concomitant medication on various parameters has been included in this study and where performed the results are presented in the appropriate section of [Section 11](#).

**Table 4 CYP1A2: Substrates, Inhibitors, Inducers**

Inhibitor	Drug Class
Amlodipine	Calcium channel blocker (dihydropyridine) + ACE inhibitor
Cimetidine	H2 blocker
Ciprofloxacin	Antibiotic
Fluvoxamine	Antidepressants
Fospropofol	Short acting hypnotic/sedative/anesthetic agent
Gemfibrozil	Lipid-regulating agent
Ketoconazole	Anti-fungal
Diclofenac	NSAID
Methoxsalen	8-methoxypsoralens
Mexiletine	Anti-arrhythmic
Miconazole	Anti-fungal
Nifedipine	Calcium channel blocker
Norfloxacin	Antibiotic (fluoroquinolones)
Propofol	Systemic general anesthetic
Primaquine	Antimalarial agent
Ofloxacin	Antibiotic (fluoroquinolones)
Thiabendazole	Anthelmintic agent
Tranylcycromine	Antidepressant
Zileuton	Anti-leukotriene, anti- asthmatic agent
Inducer	Drug Class
Carbamazepine	Anticonvulsant
Phenobarbital	Barbiturate
Primidone	Barbiturate/anticonvulsants
Rifampin	Antimycobacterial agent
Substrate	Drug Class
Acenocoumarol	Anticoagulant
Alosetron	Antagonist action on the 5-HT3 receptors
Aminophylline	Xanthine
Betaxolol	Beta blocker
Caffeine	Central nervous system stimulant
Clomipramine	Antidepressant
Clozapine	Anti-psychotic agent
Cyclobenzaprine	Muscle relaxant
Dacarbazine	Anti-cancer agent
Duloxetine	Antidepressant
Estradiol	Hormonal agent
Estrogens, conjugated A/synthetic	Hormonal agent

**Table 4 CYP1A2: Substrates, Inhibitors, and Inducers (continued)**

Substrate	Drug Class
Estrogen, conjugated equine	Hormonal agent
Estrogen, esterified	Hormonal agent
Estropipate	Hormonal agent
Flutamide	Hormone/anti-androgene
Fluvoxamine	Antidepressant
Guanabenz	Alpha-2 adrenergic agonist
Mexiletine	Anti-arrhythmic agent
Mirtazapine	Antidepressant
Olanzapine	Atypical anti-psychotic agent
Pimozide	Anti-psychotic agent
Propranolol	Beta blockers/antihypertensive
Ramelteon	Melatonin receptor agonist/insomnia medication
Rasagiline	Anti-Parkinson's drug
Riluzole	Anticonvulsant
Ropinirole	Anti-Parkinson's drug
Ropivacaine	Local anesthetic drug
Tacrine	Anti-Alzheimer Drug
Theophylline	Calcium channel blocker
Thiothixene	Anti-psychotic
Tizanidine	Skeletal muscle relaxant
Trifluoperazine	Anti-psychotic

Data source:[22].

**Table 5 CYP2A6: Substrates, Inhibitors, Inducers**

Inhibitor	Drug Class
Amiodarone	Anti-arrhythmic agent
Desipramine	Antidepressant
Isoniazid	Anti-bacterial drug
Ketoconazole	Anti-fungal agent
Letrozole	Anti-estrogen drug
Methoxsalen	Systemic psoralens
Miconazole	Anti-fungal medication
Tranylcypromine	Antidepressant
Inducer	Drug Class
Amobarbital	Barbiturate
Pentobarbital	Barbiturates
Phenobarbital	Barbiturates/anticonvulsants
Rifampin	Anti-mycobacterials
Secobarbital	Barbiturates
Substrate	Drug Class
Dexmedetomidine	Alpha 2-Adrenoceptor, sedative
Ifosfamide	Anti-cancer, alkylating agents

Data source:[22].

Medication containing estrogens (e.g., for contraception and for hormone replacement therapy), even though known to be CYP1A2 inhibitors, were allowed in this study but were documented on the CRF.

9.4.12 Compliance to Investigational Product

During the Confinement Period, compliance for all study arms was ensured by strict dispensation of the products (product by product) and collection of used THS Menthol Tobacco Sticks/mCC butts was documented in an appropriate log.

During the Ambulatory Period, subjects in the 3 study arms captured, from Discharge on Day 6, until 11:00 PM on Day 90, the number of product used (e.g., menthol and non-menthol CC, THS Menthol Tobacco Sticks, or any other tobacco/nicotine containing products including NRT) on a daily basis in the product use electronic diary. The product use electronic diary was supplied by the Sponsor and distributed to the subjects by the study site collaborator. The product use electronic diary served as a compliance tool in the 3 arms. On Day 6, compliance to the product was ensured by the merge of the accountability log (from 06:30 AM to Discharge) and the product use electronic diary. In case of discrepancy between the log and the electronic diary entries, the electronic diary entries were considered as source data.



In addition, in the SA arm, compliance was chemically verified using an exhaled CO breath test during both the Confinement and Ambulatory Periods. The cut-off point for the CO breath test value to distinguish mCC use versus no mCC use was 10 ppm [23]. No subjects from the SA arm were discontinued from the study if their exhaled CO breath test results were >10 ppm.

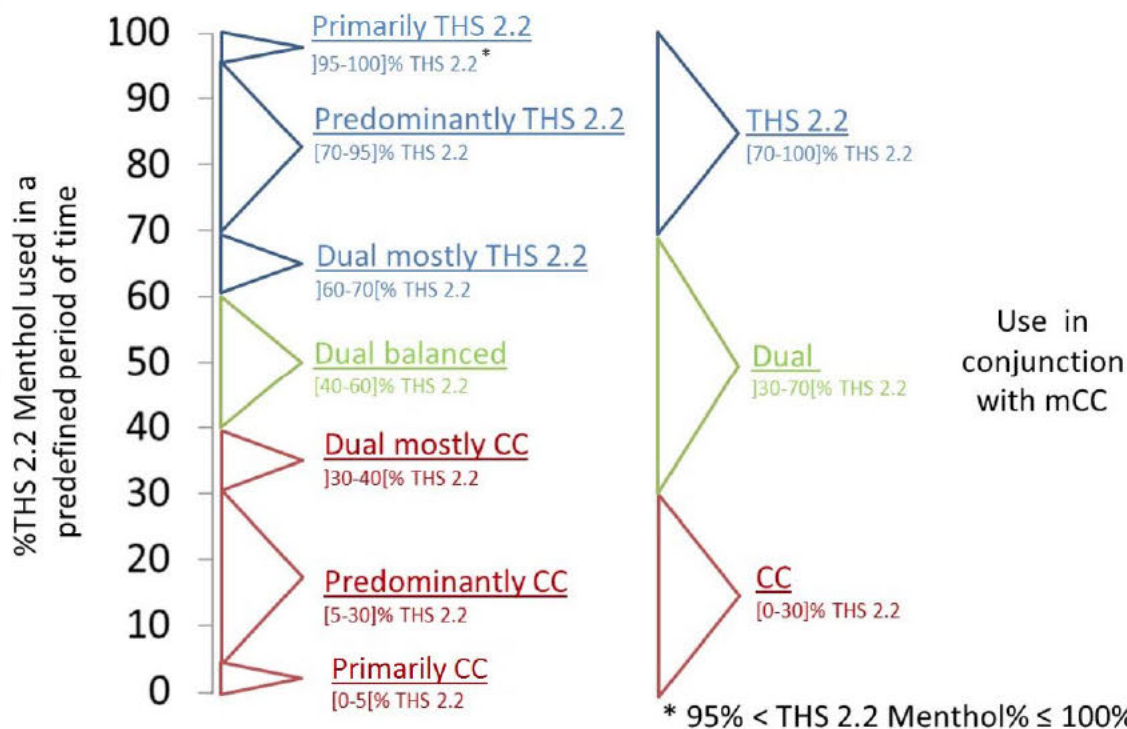
9.4.12.1 Dual-Use

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

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

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

Product use categories are summarized in Table 10, and Figure 2 presents a detailed overview of their definition.

**Figure 2 Product Use Pattern Categorization**

The more granular categorization scheme was used for the definition of the Per Protocol (PP) Set and for the description of the product use patterns observed in the study whereas the less granular scheme was used for the presentation of other study endpoints (e.g., safety endpoints) to better understand the impact of product (see [Section 11.4.4](#) for further details).

9.4.12.2 Abstinence from mCC Use

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

- “Abstinence”: full abstinence from tobacco or nicotine containing product use other than the assigned product, biochemically verified with CO breath test ≤ 10 ppm.
- “Predominantly abstinence”: no more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average and no more than 2 uses on a single day.



- “Not abstinent”: more than 0.5 uses of any tobacco or nicotine containing product (other than the assigned product) per day on average or more than 2 uses on a single day.

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 as described in [Section 9.4.13.1](#) and [Section 9.4.13.2](#), respectively.

9.4.13.1 Smoking Restrictions and Restrictions to the Smoking Abstinence Arm

9.4.13.1.1 Confinement Period

To avoid smoke cross contamination between the 3 study arms, subjects used THS 2.2 Menthol and smoked mCC in separate rooms and subjects allocated to the SA arm did not have access to the smoking rooms. All precautions were taken to remove any temptation to smoke for subjects who were randomized to the SA arm.

In the THS 2.2 Menthol and SA arms, subjects were not allowed to smoke any mCC or use any nicotine/tobacco-containing products (including NRT) from Day 1 (06:30 AM) until Discharge on Day 6. In the mCC arm, subjects were not allowed to use the THS 2.2 Menthol, any nicotine/tobacco-containing products other than mCC brought to the site by the subject. In the SA arm, intensive support including psychological support was provided upon the request of the subject, Principal Investigator, or study site collaborator.

Smoking was only allowed during the designated smoking times, from 06:30 AM to 11:00 PM. Smokers did not have free access to their mCC or THS 2.2 Menthol; these were dispensed by the study collaborator individually as described in [Section 9.4.7](#).

From Admission on site, smoking was not allowed during assessments on the Admission Day at the discretion of the site. Smoking was allowed on Day 6 after CYP2A6 activity measurements, assessment of cough and MNWS questionnaire completion, and spirometry had been conducted.

In general, the performance of scheduled procedures had priority over the wish of a subject to use the product. However, this was different on Day 5 due to the assessment of the nicotine profile. If the subject wanted to use the product on Day 5 around the time of the blood draw, he/she was allowed to use the allocated product first and the blood was drawn thereafter.



9.4.13.1.2 Ambulatory Period

Subjects in the THS 2.2 Menthol arm were instructed to exclusively use THS 2.2 Menthol and subjects in the SA arm were instructed to remain abstinent from smoking with or without NRT. Subjects in the SA arm were able to use NRT if considered necessary by the Investigator or if required by the subject. Nicotine replacement therapy products were used as per the product label, and could have been purchased by subjects at a pharmacy. Subjects were then reimbursed. Intensive support including psychological support was provided upon the request of the subject, or of the Principal Investigator, or study collaborator.

Product use was allowed during the Ambulatory Visits from 08:00 AM to 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, and Day 61, product use was allowed from 06:30 AM. However, in the morning of Day 91, smoking was not allowed until assessment of cough and MNWS questionnaires completion, and CYP2A6 activity measurements, and spirometry had been performed on site.

9.4.13.2 Dietary Restrictions

9.4.13.2.1 Confinement Period

A standard diet was designed by a dietician. For each meal, the caloric and fat content was controlled in order to avoid a “high-fat” diet. The FDA guidance on food-effect studies for bioequivalency testing identified a “high-fat” diet as a diet which maintained approximately 50% of total caloric content of the meal and was high in calories (approximately 800 to 1000 calories) [24].

In order to avoid any effect on assessment of BoExp, grilled or pan-fried meat, smoked pre-cooked meats (e.g., tuna, ham, corned beef, and meats), smoked bacon and sausage was not permitted. In addition, to avoid any effect on the measurement of CYP1A2 activity, alcohol, broccoli, Brussel sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana etc.) were forbidden [13] except for the intake of the CAF tablet for CYP1A2 measurement. Consumption of quinine-containing drinks (e.g., tonic water) was also forbidden.

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 (see [Appendix 16.1.1](#)). Additional light snacks, fruits, and raw vegetables were 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. In addition for the purpose of the Ames test planned on Day 0 and Day 5, the menus served on Day-1 and Day 4 were identical.



Fasting state was observed for at least 10 hours prior to blood draws for the safety laboratory (at the Screening Visit, Day 0, and Day 6), CREs in serum/plasma/blood (Day 0 and Day 6), for the serum/plasma bio-banking samples for further BoExp/CREs (at the Screening Visit, Day 0, and Day 6), and for blood bio-banking samples for transcriptomics (Day 0 and Day 6).

9.4.13.2.2 Ambulatory Period

The above dietary restrictions were not applicable for the Ambulatory Period. However, 3 days prior to the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, and during visits on site, subjects were asked by the study collaborators to refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussel sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) were not allowed on site during the Ambulatory Visits.

Fasting state was observed for at least 10 hours prior to blood draws for the safety laboratory (Day 31, Day 61, and Day 91), risk factors assessments in serum/plasma/blood (Day 31, Day 61, and Day 91), serum/plasma bio-banking samples for further analysis of BoExp and CREs (Day 91), and for blood bio-banking for transcriptomics (Day 91).

9.5 Study Variables Assessed and Schedule of Events

Personnel who conducted the study measurements or recordings had appropriate training, which was fully documented. Quality and control measures were in place. An overview of all study procedures is shown in the schedule of events (see [Table 8](#)).

Due to logistical reasons, it was not reasonable for all subjects to have study assessments/procedures at the same time. Therefore, adequate time windows were permitted for each study procedure at each time point (see Section 9 of the protocol [[Appendix 16.1.1](#)] and Section 11.1.3 of the SAP [[Appendix 16.1.8](#)]). Study collaborators adhered to the study site's Standard Operating Procedures (SOPs) for all activities relevant to the quality of the study.

9.5.1 Biomarker Assessments

Precautions were taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine or CO, in accordance with the laboratory and sampling handling manual.

9.5.1.1 Biomarkers of Exposure

9.5.1.1.1 Urinary Biomarkers of Exposure

The following BoExp were measured in 24-hour urine collection samples as per [Table 9](#):



- The BoExp for the primary objective: MHBMA, 3-HPMA, S-PMA, and Total NNAL.
- The BoExp for the secondary objective: Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, NEQ, CEMA, 3 hydroxybenzo(a)pyrene, HEMA, S-BMA, and HMPMA.

Urinary BoExp were measured in 24-hour urine samples during the Confinement Period from Day -1 to Day 5, and during the Ambulatory Period collected at the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit.

In [Table 9](#), for the 24-hour urine collection samples, the dot corresponds to the day on which the 24-hour urine collection period started. For example, NEQ measured on Day 5 in the 24-hour urine collection started on Day 5 and ended 24 hours later on Day 6. At Discharge on Day 6, subjects emptied their bladder shortly before 06:29 AM and this was the last urine collection for the 24-hour urine for the Day 5 dot mark in [Table 9](#).

For normalization of BoExp, creatinine was also measured in the 24-hour urine samples.

9.5.1.1.2 Exhaled CO and Carboxyhemoglobin

Carboxyhemoglobin measured in blood and exhaled CO was investigated as a measure of CO in all 3 study arms. The CO breath test was conducted in conjunction with the blood sampling for COHb, where applicable. In the SA arm, the CO breath test served as a verification of compliance (see [Section 9.4.12](#)).

Carbon Monoxide Breath Test

Carbon monoxide in exhaled breath was measured using the Micro+™ Smokerlyzer for all study subjects.

During the Confinement Period on Day -1 to Day 5, for subjects in the THS 2.2 Menthol and mCC arms, the CO breath test was conducted 4 times per day. The first assessment for subjects in the THS 2.2 Menthol and mCC arms was conducted within 15 minutes prior to the first product use. The other 3 assessments were conducted between 12:00 PM-01:30 PM, 04:00 PM-05:30 PM, and 08:00 PM-9:30 PM.

For subjects in the SA arm from Day 1 onwards, the first CO breath test was conducted between 08:00 AM-09:30 AM. The other 3 assessments were conducted between 12:00 PM-01:30 PM, 04:00 PM-05:30 PM, and 08:00 PM-9:30 PM.

On Day -2 and Day 6, and during the Ambulatory Period at the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, the CO breath tests were conducted once, irrespective of time of product use.



Carboxyhemoglobin

Assessment for COHb measurement was performed at the local laboratory. Carboxyhemoglobin in blood was assessed on a daily basis, starting from Day -1 until Day 5.

On Day -1 to Day 4: one blood sample was collected between 08:00 PM-09:30 PM.

On Day 5: for THS 2.2 Menthol and mCC arm, one blood sample was collected within 15 minutes prior to the first product use. The 3 other blood samples were collected between 12:00 PM-01:30 PM, 04:00 PM-05:30 PM, and 08:00 PM-09:30 PM.

For subjects in the SA arm, from Day 1 onwards, the first COHb measurement was between 08:00 AM-09:30 AM. The 3 other blood samples were collected between 12:00 PM-01:30 PM, 04:00 PM-05:30 PM, and 08:00 PM-09:30 PM.

At the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit: for all study arms, 1 blood sample was collected during the visit, irrespective of the time of product use.

9.5.1.1.3 Plasma Nicotine and Cotinine

Nicotine and cotinine concentrations were measured in plasma to evaluate the exposure to nicotine in all 3 study arms. For subjects in the SA arm, only 1 blood sample was collected on Day 5 and Day 6 and no sampling for nicotine/cotinine PK profiling was conducted.

On Day 0 to Day 4 (all study arms): 1 blood sample per day was collected in the evening between 08:00 PM-09:30 PM.

Blood samples for nicotine/cotinine PK profiling were collected on Day 5 and Day 6 for subjects in the THS 2.2 Menthol and mCC arms only: in total, 9 blood samples were drawn on Day 5. The first blood sample on Day 5 was drawn within 15 minutes prior to the first product use. On Day 5, the start time of the first product use (T0) served as reference for the time to peak concentration. An additional 8 blood samples were drawn in 2 hour intervals after the start of product use. The last blood sample was drawn no later than 11:00 PM, corresponding to the end of product use. At all time points, if the subject wanted to use the product around the time of the blood draw, he/she used it first and the blood was drawn after product use. Depending on the time of the first product use, fewer than 8 blood samples could have been collected from a subject after T0. On Day 6, 2 blood samples were drawn. The first one was 20 hours after T0 and the second blood sample was 24 hours after T0 (with T0 being the start time of first product use on Day 5).



On Day 5 and Day 6 (SA arm only): on Day 5, 1 blood sample was drawn in the evening between 8:00 PM-09:30 PM and on Day 6, 1 blood sample was drawn in the morning between 08:00 AM-09:30 AM.

At the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit (all study arms): 1 blood sample was drawn during these visits, irrespective of the time of product use.

9.5.1.2 Other Assessments

9.5.1.2.1 Risk Markers

The following CREs were assessed in this study:

- Systolic and diastolic blood pressure, hs-CRP, fibrinogen, homocysteine, blood glucose, LDL cholesterol, HDL cholesterol, TG, TC, HbA1c, sICAM-1, WBC, 8-epi-PGF_{2α}, 11-DTX-B2, platelet count, weight, and waist circumference.

The assessment of systolic and diastolic blood pressure, blood glucose, TG, TC, platelet count, weight, and waist circumference were not repeated because they were part of the safety parameters/clinical evaluation. Of note, the WBC, TG, TC, and platelet parameters were derived from assessed safety parameters, and thus, a bioanalytical report was not provided for these CREs.

Selected CREs were evaluated at the following time points. Fasting state was observed for at least 10 hours prior to the assessments which required blood, serum, or plasma:

- Systolic and diastolic blood pressure: on Day 0, Day 6, Day 30, Day 60, and Day 91. The results from vital signs assessments were used.
- High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, LDL cholesterol, HDL cholesterol, TG, TC in serum: on Day 0, Day 31, Day 61, and Day 91. Sample collection was planned to measure hs-CRP, homocysteine, LDL cholesterol, HDL cholesterol at the mentioned time points and the results for blood glucose, TG, and TC from the safety laboratory panel on Day 0, Day 31, Day 61, and Day 91 were used.
- Fibrinogen in plasma: on Day 0, Day 31, Day 61, and Day 91.
- Hemoglobin A1c in serum: on Day 0, and Day 91.
- Soluble intercellular adhesion molecule-1 measured in serum: on Day 0, Day 6, Day 31, Day 61, and Day 91.
- 8-epi-prostaglandin F2 alpha and 11-DTX-B2 in 24-hour urine: on Day 0 and Day 5 and at the Day 30 Visit, Day 60 Visit, and Day 90 Visit. The results were normalized for creatinine and expressed as concentration adjusted for creatinine.
- White blood cell and platelet count in whole blood: on Day 0, Day 6, Day 31, Day 61, and Day 91. The results from the safety laboratory panel were used.



- Waist circumference and weight: on Day-2, and Day 91 as evaluated as part of the clinical examination.

9.5.1.2.2 CYP1A2 Activity Test

Cytochrome P450 1A2 activity was measured on Day 0, Day 5, and at the Day 90 Visit. Measurement of enzyme activity was based on the post-dose PX and CAF plasma molar concentrations approximately 6 hours (± 15 minutes) after the intake of 1 Tomerumin[®] [25] CAF tablet (around 170 mg CAF) with 150 mL \pm 10 mL water [13].

The exact time of intake of the CAF tablet in the morning and of blood sampling (the blood sample was taken 6 hours [± 15 minutes] after the intake of the tablet) was recorded.

9.5.1.2.3 CYP2A6 Activity

Cytochrome P450 2A6 activity was measured in plasma on Day 0, Day 6, and Day 91, using the molar metabolic ratio of *trans*-3'-hydroxycotinine and cotinine [26]. Blood sampling for CYP2A6 was done prior to product use on each day.

9.5.1.2.4 Ames Mutagenicity Test

Urine mutagenicity, a biomarker for measuring mutagen load, was measured on Day 0, Day 5, and at the Day 90 Visit in 24-hour urine. The urinary determination of each sample was assessed in 1 bacterial strain (*S. typhimurium* strain YG1024), using S9 metabolic activation and 4 doses for each of the urine extracts.

9.5.2 Safety Variables and Measurements

Safety variables were assessed in this study at the time points shown in Table 8. Safety was primarily assessed by analysis of AE data (including device malfunction or misuse); other safety variables monitored in this study included: respiratory symptoms (cough assessment VAS and Likert scales), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), spirometry, ECG data, clinical chemistry, hematology, concomitant medications, urine analysis safety panel, and physical examination (including BMI).

9.5.2.1 Adverse Events

The FDA MRTP guidelines [9] provides the following definition for AEs for tobacco products: “an AE is any health-related event associated with the use of tobacco product in humans, which is adverse or unfavorable, whether or not it is considered related to the tobacco product, as defined by the MRTP guidelines”.

An AE is defined as any untoward medical occurrence, or clinical investigation in a subject administered an IP, which does not necessarily have a causal relationship with the



IP. An AE can therefore be any unfavorable and unintended sign (including a clinically relevant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

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

A SAE was defined as, but not limited to, any untoward medical occurrence which:

- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Resulted from a congenital anomaly/birth defect.

Important medical events that did not result in death, were not life-threatening, and did not require hospitalization may have been considered an SAE when, in the opinion of the Principal Investigator, they jeopardized the subject's well-being 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 recorded as SAEs (they were recorded only as AEs). However, any AE that occurred during this pre-planned hospitalization was considered according to the above definitions.

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

The Principal Investigator was responsible for assessing and documenting all AEs during the study. Adverse events were recorded from the time of signature of the ICF onwards until End of Study either via spontaneous reporting or by the use of consistent, open, non-directive questions from the study site collaborator (e.g., "Have you had any health problems since the previous visit/How are you feeling since you were last asked?"). The main source for AE collection was the face-to-face interview with the subject, in addition AE information might have emerged from the questionnaires and the VAS.

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

For each AE the intensity was graded by the Principal Investigator on a 3-point intensity scale using the following definitions:

- Mild: The AE was easily tolerated and did not interfere with daily activity.



- Moderate: The AE interfered with daily activity, but the subject was still able to function.
- Severe: The AE was incapacitating and required medical intervention.

All AEs were assessed by the Principal Investigator or designee as either 'related' or 'not related' to the IP and/or study procedures according the following definitions:

- Not related: The temporal relationship of the clinical event to IP 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 study IP 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, 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 administration or study procedures, and of the expectedness of an AE are provided in the protocol ([Appendix 16.1.1](#)).

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

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

Any occurrences of THS Tobacco Stick Holder or THS Charger misuse (use not in accordance with its label and instruction), or malfunction, were documented by the Principal Investigator using a device issue log. Any malfunctions of the THS Tobacco Stick Holder or Charger that lead to an AE/SAE were analyzed as such.

9.5.2.2 Physical Examination

A physical examination (including body weight) was conducted at the Screening Visit, at Admission (Day -2), at Discharge on Day 6, on Day 30, Day 60, and Day 91. Appropriate medical advice was provided to the subjects in case of any medical findings requiring health care.



Body height was measured at Screening only. Waist circumference was measured at Admission (Day -2) and on Day 91 only. Screening values were used to calculate values for BMI using the following formula.

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

9.5.2.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate were measured at the Screening Visit, at Admission (Day -2), in the morning of every day of the Confinement Period (i.e., Days -1 to 6), and at each Ambulatory Visit (on Day 30, Day 60, and on Day 91). All measurements were made after the subject had rested for at least 5 minutes in a supine position. For every measurement, it was documented, as a deviation, if the subject had smoked within 15 minutes prior to the measurement.

9.5.2.4 Clinical Laboratory Parameters

Hematology, clinical chemistry, and urine analysis for the safety panel were measured at Screening, Day 0, Day 6, Day 31, Day 61, and Day 91, irrespective of product use. Blood samples were taken 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. Parameters measured are listed in [Table 6](#). The methodology for measuring albumin changed during the study. Further details are provided in a Note to File ([Appendix 16.1.1](#)).

**Table 6 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 aminotransferase	
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	

9.5.2.5 Electrocardiogram

A standard 12-lead ECG was recorded at Screening, on Day 6, Day 30, Day 60, and Day 91. The ECG testing was performed as per the site's local practice. A standard 12-lead ECG 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 machine according to Bazett's formula. Every ECG was assessed as normal, abnormal non-clinically relevant, or clinically relevant. A diagnosis was provided on the CRF for all ECGs assessed as abnormal – clinically relevant. All ECG print-outs were interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper were photocopied and stapled together for inclusion in the source documents.

9.5.2.6 Urine Drug Screen

A urine drug screen was performed at the study site at the Screening Visit and at Admission (Day -2). The urine was screened for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.



9.5.2.7 Breath Alcohol Test

Subjects underwent breath alcohol testing at the Screening Visit and at Admission (Day -2) using an alcometer device.

9.5.2.8 Medical History and Previous Medications

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

Prior medication taken 4 weeks prior to the Screening Visit and any concomitant medication was documented. Any medication which was 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. This applied to both prescription and over-the-counter products.

9.5.2.9 Urine Pregnancy Tests

All female subjects underwent pregnancy testing at the Screening Visit, at Admission (Day -2), on Day 6, Day 31, Day 61, and Day 91. Female subjects with a positive pregnancy test at the Screening Visit or at Admission were considered a Screening failure and not enrolled. The product test at Admission was conducted only in female subjects with a negative urine pregnancy test.

In any case of a positive urine pregnancy test, the Principal Investigator informed the subject about the risks associated with smoking during pregnancy. In the event of an unclear urine pregnancy test, absence of pregnancy was confirmed by a serum follicle stimulating hormone level >20 IU/L.

Any pregnancies detected during the study were reported and handled as described in the protocol ([Appendix 16.1.1](#)).

9.5.2.10 Serological Tests

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



9.5.3 Other Clinical Assessments

9.5.3.1 Urine Cotinine Screening Test

A urine cotinine test was performed at Screening and at Admission (Day -2) in order to confirm the subject's smoking status. The test detected cotinine with a cotinine threshold of ≥ 200 ng/mL, indicating that the subject was a smoker.

9.5.3.2 Chest X-ray

A chest X-ray (anterior-posterior and left lateral views) were 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 could present a chest X-ray with anterior-posterior and left lateral views at the Screening Visit which was not older than 6 months.

9.5.3.3 Spirometry

Spirometry with and without a short acting bronchodilator was performed at the Screening Visit to evaluate inclusion/exclusion criteria (the post-bronchodilator results). At Screening, spirometry without bronchodilator was performed first followed by spirometry with bronchodilator. At Screening, spirometry was conducted at least 1 hour after smoking. Furthermore, spirometry without bronchodilator was performed prior to product use on Day 0 (baseline values), and on Day 6 and Day 91 (for comparison with the baseline values).

All personnel performing lung function testing had appropriate training, and QC measures were put into place and were properly documented (including calibration records) and filed at the pulmonary function laboratory. Spirometry with maximum voluntary ventilation measurement was performed and FEV₁ and FVC were recorded.

9.5.3.4 Demographic Data

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

9.5.3.5 Identification of the Current Cigarette Brand

Identification of the current mCC brand(s) smoked by the subject was performed 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. At Admission (Day -2), subjects handed their mCC supply for the entire Confinement Period to the study collaborators. The study collaborator documented the brand name and yields. A photograph of the front and the side of the cigarette pack supplied by the subject (bearing the tar and nicotine yields) was taken by the study collaborators in addition to recording the brand name and yield. These



photographs were considered source documentation. A copy of the photographs were provided to, and received by the Sponsor electronically on Compact Disc.

9.5.3.6 Smoking History and Willingness to Quit Smoking

Subjects were asked about their smoking history at Screening and Admission (Day -2). This included questions to evaluate whether the subject had smoked for at least the last 3 consecutive years, to determine the number of mCC smoked during the previous 4 weeks, and to check if the CCs smoked during the previous 4 weeks were mCCs. At the Screening Visit only, the subject was also asked if he/she planned to quit smoking within the next 3 months. In addition, the subject was asked if he/she had used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT), electronic cigarettes, or similar devices, within 4 weeks prior to assessment.

At Screening and Admission (Day -2), subjects were also asked if they were ready to abstain from smoking for up to 90 days (as required in the study protocol inclusion criteria). Only subjects who were prepared and able to comply with this requirement were considered for participation in the study.

9.5.3.7 Demonstration and Trial of the THS 2.2 Menthol

All subjects were given a demonstration of the THS 2.2 Menthol product at the Screening Visit. On Day -2, as the last procedure of the eligibility assessments on that Day, subjects were offered a product test of the THS 2.2 Menthol (using of up to 3 THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol product trial was only performed after pregnancy was excluded by a negative urine pregnancy test. Only subjects who were willing and able to use the product could participate in the study.

9.5.3.8 Product Preference

In order to perform a complementary analysis on subjects' preference, the following question was asked to all subjects on Day -2 after enrollment: "Which product would you prefer to be randomized to: THS 2.2 Menthol, mCC, SA, or no preference?"

9.5.4 Bioanalytical Methods

All bioanalytical assays and laboratory assessments were carried out using validated methods as documented in the bioanalytical reports ([Appendix 16.1.9](#)). Precautions were taken during blood sampling and processing to prevent the contamination of samples with environmental smoke. Of note, WBC, TG, TC, and platelet parameters were derived from assessed safety parameters, and thus, a bioanalytical report was not provided for these CREs or other assessed safety parameters.

Analytical laboratory details are presented in [Section 6](#).



9.5.5 Sample Collection Storage and Shipping

Biomarkers of exposure in blood, selected BoExp in urine, and plasma samples were tested as described in [Section 6](#) by Celerion with the exception of COHb blood samples and the safety laboratory panel which were tested at Covance Central Laboratory Services, Geneva, Switzerland; (b) (4)

The urine pregnancy tests, urine drug screen, and urine cotinine tests were performed on-site by study-site personnel.

Detailed procedures for sample collection and handling of samples are described in a separate sample handling manual. Details relating to the destruction of samples are available in the protocol ([Appendix 16.1.1](#)).

9.5.5.1 Blood Samples

Blood samples were collected by qualified and trained site personnel with subjects in a seated position during blood collection. The maximal total volume of blood drawn for each subject was around 290 mL, which included 50 mL for safety and repeated analysis, 30 mL for long-term storage of the bio-banking samples for further analysis of BoExp and CREs (only if additional consents were given) and 15 mL for long-term storage bio-banking samples for further analysis of transcriptomics (only if additional consents are given) (see [Section 5.4](#)). The blood sampling for transcriptomics and the data related to these samples were anonymized.

9.5.5.2 Urine Samples

Spot urine samples were used for the urine drug screen, urine cotinine screen, urine pregnancy test, and safety urinalysis.

For 24-hour urine collection during the Confinement Period: subjects emptied their bladders shortly before 06:30 AM on the study day indicated in [Table 9](#). The collection period started at 06:30 AM and ended on the following day at 06:29 AM. Shortly before 06:29 AM, after nearly 24 hours of urine collection, subjects emptied their bladder again and this urine was used as the final collection of the 24-hour urine sample.

At Discharge on Day 6, subjects emptied their bladder shortly before 06:29 AM. This was the last urine collection collected for the 24-hour urine for the Day 5 dot mark in [Table 8](#).

For 24-hour urine collection during the Ambulatory Period: the 24-hour urine fraction was collected at the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit) on site. Subjects were asked to arrive at the site around 08:00 AM on Day 30, Day 60, and Day 90 and remained overnight on site until Day 31, Day 61, and Day 91, respectively. Subjects emptied their bladder on Day 30, Day 60, and Day 90 shortly before 09:00 AM and this urine was discarded. The collection period started at 09:00 AM \pm 20 minutes.



After nearly 24 hours of urine collection the following day at 08:59 AM \pm 20 minutes, subjects emptied their bladder again and this urine was used as the final collection of the 24-hour urine sample.

For both Confinement and Ambulatory Periods: all urine passed during the sampling period was collected and put into the sampling bottle, with the exception of about 10 mL for the spot urine tests (described above). No urine was passed into the toilet. The volume of 24-hour urine, and the start and end time of urine collection was recorded by the study collaborators.

For assessment of urine BoExp creatinine for normalization of urine BoExp, 8-epi-PGF₂ α and 11-DTX-B2, sample bio-banking and urine mutagenicity, aliquots from the 24-hour urine collection were taken as planned.

Details regarding the processing of the 24-hour urine samples were provided in a separate Celerion sample handling manual.

9.5.5.3 Bio-banking

All samples collected for bio-banking were collected only when subjects had signed the ICF. If a subject gave consent for sample bio-banking for further analysis of BoExp/CREs, additional samples of urine (from the 24-hour urine collection) and serum/plasma (30 mL of blood in total) were collected as follows:

- Samples from the 24-hour urine were collected from the urine collections that started on Day 0, Day 5, and at the Day 90 Visit (10 tubes of 10 mL each per time point).
- Serum/plasma were collected on Day 0, Day 6, and Day 90 Visit (30 mL of blood in total, with 2 tubes of 5 mL of blood drawn per time point: from one tube 2 x 1 mL plasma, and from the second tube 2 x 1 mL of serum were collected and stored).

If a subject gave consent for sample bio-banking of whole blood for further transcriptomics analysis, a total of 15 mL of blood was collected as follows: blood was collected on Day 0, Day 6, and at the Day 90 Visit (5 mL per time point and each 5 mL sample was further split into 2 tubes of 2.5 mL each).

The samples intended for sample bio-banking were kept frozen, separate from the other samples collected, and were shipped to a central storage facility according to the sample handling manual. After the final Clinical Study Report (CSR) was signed, samples of plasma/serum/blood were stored for a maximum of 5 years and samples of urine were stored for a maximum of 2 years. The blood bio-banking for transcriptomics were stored for a maximum of 5 years. The facility at which the samples were stored followed their procedures for destruction of banked samples if a subject withdrew their consent for coded sample bio-banking.



9.5.6 Other Study Procedures

9.5.6.1 Product Use Diary

A product use electronic diary was used for the documentation of used THS Menthol Tobacco Sticks, smoked CCs (menthol and non-menthol), used NRTs product, or the use of other nicotine/tobacco-containing products. All subjects (including those subjects randomized to the SA arm) completed this diary on a daily basis from Discharge on Day 6 until 11:00 PM on Day 90. Subjects were trained by the study collaborators in the use of the electronic diary during the Confinement Period at the time the diary was delivered to the subject by the study collaborator (Day 6).

9.5.6.2 Human Smoking Topography Assessment

Human smoking topography involved the measurement of each smoker's unique way of smoking mCCs or using THS Menthol Tobacco Sticks. The HST SODIM[®] device, model SPA/M (SODIM[®] Instrumentation, Fleury les Aubrais, France) was used to measure smoking topography. It consisted of a special sample holder (containing a constriction in the middle) which was placed between the smoker's mouth and the filter of the mCC or menthol THS Tobacco Stick. The Holder was connected by 2 narrow tubes to a portable data recording system.

On Day 0, the HST SODIM[®] device was used for all mCC smoked for all subjects. On Day 1 and Day 4 of the Confinement Period, the HST SODIM[®] device was used for every smoking event for all subjects in the mCC and THS 2.2 Menthol arms. On Day 30, Day 60, and Day 90 of the Ambulatory Period, HST SODIM[®] device use started between 08:30 AM and 09:30 AM and was used for every mCC or stick used in the following 4 hour window.

Smoking topography with the HST SODIM[®] device was not performed in subjects smoking mCC that were incompatible with the HST SODIM[®] device (e.g., slim mCC). For subjects in the SA arm, no HST assessments were performed.

For each subject, 1 HST SODIM[®] device was assigned on Day -1 which was used by that subject on all HST assessment days (in the case of malfunction, the device was exchanged). In the mCC arm, a HST SODIM[®] device was assigned to all subjects smoking non-slim mCCs.

The Sponsor provided training on the use of the HST SODIM[®] device to the study collaborators who, in turn, provided training to the subjects. All HST SODIM[®] devices were returned to the Sponsor after completion of the study.



The HST SODIM[®] device measured and recorded the flow and other per-puff parameters listed in [Table 15](#). From the per-puff parameters ([Table 15](#)), the per-cigarette parameters shown in [Table 16](#) were derived (representing average values or totals per-cigarette).

Prior to calculation of the per-cigarette parameters, the Sponsor HST group validated the data and discarded any invalid data. Only valid data for the per-cigarette parameters were part of the study database and were analyzed.

9.5.6.3 Visual Inspection of Tobacco Plugs

All tobacco plugs collected during the study were sent to the Sponsor for subsequent visual inspection at the PMI laboratories to determine whether combustion occurred during product use.

9.5.6.4 THS Filter Analysis

All filters from used THS Menthol Tobacco Sticks were sent to an external laboratory (Labstat International ULC; [Section 6](#)) for analysis. All filters from used THS Menthol Tobacco Sticks were collected from Day 1 to Day 5. No filter analysis was performed during the Ambulatory Period.

9.5.6.5 Questionnaires

The subject questionnaires and the VAS used in this study were entered by the subject directly in an electronic patient reported outcomes device or on paper copy.

Symptoms or worsening of symptoms documented on any of the questionnaires or the VAS were not necessarily documented as additional AEs because the questionnaire and the VAS were analyzed as part of the final report. However, it was at the discretion of the Principal Investigator to decide whether to document such symptoms as additional AEs. The main source for AE collection was the face-to-face interview between the subject and study collaborators, using open, non-directive questions (see [Section 9.5.2.1](#)).

9.5.6.5.1 Fagerström Test for Nicotine Dependence

Potential nicotine dependence was assessed via a questionnaire at Screening and on Day 90 using the FTND [\[27\]](#).

The questionnaire consisted of 6 questions which were answered by the subject himself/herself. The scores obtained on the test permitted the classification of nicotine dependence into 3 levels: mild (0-3 points), moderate (4-6 points), and severe (7-10 points) [\[28\]](#).



9.5.6.5.2 Assessment of Cough

Subjects were asked to assess the respiratory symptom 'cough' on a VAS, on 3 Likert scales, and with an open question on a daily basis during the Confinement Period (from Day 0 to Day 6), and at every visit on Day 31, Day 61, and Day 91. From Day 0 to Day 6 only, assessment of cough was performed prior to start of product use/smoking and no later than 10:00 AM. At the Day 30 Visit and the Day 60 Visit, assessment of cough was conducted irrespective of the time of product use but no later than 10:00 AM. At the Day 90 Visit (Day 91), assessment of cough was conducted prior to smoking but no later than 10:00 AM.

Subjects were asked if they had experienced a regular need to cough, e.g., whether they had coughed several times in the previous 24 hours prior to assessment. If the answer was 'yes', subjects were asked to complete a VAS, 3 Likert scales, and to answer the open question.

On the VAS, subjects assessed how bothersome their cough was during the previous 24 hours from 'not bothering me at all' to 'extremely bothersome.'

Furthermore, subjects assessed the intensity and frequency of cough and the amount of sputum production during the previous 24 hours on Likert scales (Table 7):

Table 7 Cough Assessment Likert Scales

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

Finally, subjects were asked with an open question if they wanted to share any other important observations with the study collaborators about their coughing.



Symptoms or worsening of symptoms that were documented on any of the questionnaires or the VAS were to be documented as AEs at the discretion of the Principal Investigator (see [Section 9.5.2.1](#)).

9.5.6.5.3 Modified Cigarette Evaluation Questionnaire

Product evaluation was assessed using the MCEQ [29]. The MCEQ assessed the degree to which subjects experienced the reinforcing effects of smoking, by measuring:

- Smoking satisfaction (satisfying, tastes good, enjoys 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).

The MCEQ was completed by subjects during the Confinement Period on a daily basis from Day -1 to Day 5 and at every Ambulatory Visit on Day 30, Day 60, and Day 90. On each occasion, the MCEQ was completed between 08:00 PM and 11:00 PM. On Day -1 and Day 0, the subjects completed the questionnaire. From Day 1 onwards, only subjects who were randomized to the THS 2.2 Menthol and mCC arms completed this questionnaire.

9.5.6.5.4 Questionnaire of Smoking Urges

To assess the urge-to-smoke, all subjects were asked to fill-in a 10-item brief version of the QSU [30]. The QSU-brief is a self-reported questionnaire with 10 items 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 QSU-brief was completed by the subject himself/herself on a daily basis from Day -1 to Day 5, and on every visit during the Ambulatory Period, i.e., Day 30, Day 60, and Day 90. On each occasion, the QSU-brief was completed between 08:00 PM and 11:00 PM.

9.5.6.5.5 Minnesota Nicotine Withdrawal Scale

The MNWS revised version is a valid and reliable scale that has been used previously to examine signs and symptoms of withdrawal from cigarette smoking [31, 32]. It consists of 2 scales: a 'self-report scale' and an 'observer scale.'

For the purpose of this study, only the self-reporting scale was used and filled-in by the subject. Furthermore, the subject's weight was not recorded for the purpose of the



MNWS. At the end of the assessment of the questionnaire, the subject's pulse rate was recorded.

Subjects were asked to rate the items for the previous 24 hours on a scale ranging from 0 to 4 (where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe).

The MNWS (revised version) was completed on a daily basis from Day 0 to Day 6, and at every visit during the Ambulatory Period, i.e., Day 30 Visit, Day 60 Visit, and Day 90 Visit. From Day 0 to Day 6 only, the MNWS questionnaire was asked prior to the start of product use/smoking and no later than 10:00 AM. On Day 31 and Day 61, assessment of MNWS was conducted irrespective of the time of product use but no later than 10:00 AM. On Day 91, assessment of MNWS was conducted prior to smoking but no later than 10:00 AM.

9.5.6.5.6 Human Smoking Topography Questionnaire

A specific questionnaire, used for exploratory purposes has been developed to evaluate the impact of the use of the HST SODIM[®] device on smoker's smoking/inhalation experience in terms of ritual disruption.

This is a questionnaire with 5 items rated on a 5-point scale and open questions. Subjects were asked by the Principal Investigator to complete the HST questionnaire on:

- Day 0, between 08:00 PM and 11:00 PM, for all subjects smoking mCC compatible with the HST SODIM[®] device (i.e., non-slim mCC).
- Day 4, Day 30, Day 60, and Day 90, between 08:00 PM and 09:30 PM, for all subjects in the THS 2.2 Menthol and mCC arms (except mCC which are not compatible with the HST SODIM[®] device).

9.5.6.5.7 Socio-economic Status Questionnaire

Based on prior tobacco research socio-economic status (SES), along with age, sex, ethnicity, and tobacco use history are factors that have been shown to be related to nicotine dependence and product reinforcing value. On Day 4, subjects were asked a series of questions related to their education, occupation, size and monthly income of their household. These data allowed the Sponsor to characterize the subject household's SES.

9.5.7 Schedule of Events

Table 8 presents the schedule of events for the entire study period, and Table 9 presents the 24-hour urine collection schedule.


Table 8 Schedule of Events (continued)

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up ^v
												Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days	
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6	30	31	60	61	90	91	91 to 119
B/U: Hematology, clinical chemistry, urine analysis ^e	•			•						•		•		•		•	
Electrocardiogram	•									•	•		•			•	
Chest X-ray ^f	•																
B: HIV, hepatitis B and C	•																
U: Urine drug screen, urine cotinine screening test	•	•															
U: Pregnancy test	•	•								•		•		•		•	
Alcohol breath test	•	•															
FTND	•														•		
Smoking history	•	•															
Willingness to quit smoking in the next 3 months	•																
Readiness to abstain from smoking for up to 90 days	•	•															
Identification for mCC	•	•															
THS 2.2 Menthol demonstration	•																
THS 2.2 Menthol product test ^g		•															
Collection of mCC butts for accountability			•	•	•	•	•	•	•	•							


Table 8 Schedule of Events (continued)

	Screening	Confinement Period								Ambulatory Period							Safety Follow-up ^v
											Day 30 Visit ± 3 days		Day 60 Visit ± 3 days		Day 90 Visit ± 3 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6	30	31	60	61	90	91	91 to 119
U: Risk markers: 8-epi-PGF _{2α} and 11-DTX-B2 ^a				•					•		•		•		•		
1 caffeine tablet (170 mg)				•					•						•		
B: CYP1A2 activity				•					•						•		
B: CYP2A6 activity				•						•						•	
Product use diary ^o										•	•	•	•	•	•		
QSU-brief questionnaire ^p			•	•	•	•	•	•	•		•		•		•		
MNWS (revised version) ^q				•	•	•	•	•	•	•		•		•		•	
MCEQ (modified version; THS 2.2 Menthol and mCC arms) ^r			•	•	•	•	•	•	•		•		•		•		
HST (THS 2.2 Menthol and mCC arms) ^s				•	•			•			•		•		•		
HST questionnaire				•				•			•		•		•		
Assessment of cough ^t				•	•	•	•	•	•	•		•		•		•	
Product preference questionnaire		•															
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
U: Bio-banking for BoExp and risk markers ^u				•					•						•		
B: Bio-banking for BoExp and risk markers ^u				•						•						•	
B: Bio-banking for transcriptomics ^u				•						•						•	

Abbreviations: 8-epi-PGF_{2α} = 8-epi-prostaglandine F2 alpha; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; B = blood sample required; BMI = body mass



index; BoExp = biomarkers of exposure; mCC = menthol conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP = cytochrome P450 enzyme; FTND = Fagerström Test for Nicotine Dependence; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; HST = human smoking topography; HIV = human immunodeficiency virus; hs-CRP = high sensitive C-reactive protein; LDL = low density lipoprotein; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence; SAE = serious adverse event; sICAM-1 = soluble intercellular adhesion molecule-1; THS = Tobacco Heating System; U = urine sample required; TC: total cholesterol; TG: triglycerides.

- ^a Systolic and diastolic blood pressure, pulse rate, and respiratory rate (systolic and diastolic blood pressure were also evaluated also as risk markers on Day 0, Day 6, Day 30, Day 60, and Day 91).
- ^b Including height (only at Screening), body weight and calculated BMI. Weight was evaluated also as risk marker on Day 0 and Day 90 Visit (Day 91).
- ^c Waist circumference was evaluated also as risk marker on Day -2 and Day 90 Visit (Day 91).
- ^d At Screening, spirometry without bronchodilator was performed first, and then spirometry with bronchodilator. At Screening, spirometry was conducted at least 1 hour after smoking. Furthermore, spirometry without bronchodilator was performed prior to product use on Day 0 (baseline values), on Day 6, and Day 90 Visit (on Day 91 for comparison with the baseline values).
- ^e White blood cell, platelet count, from the safety laboratory panel evaluated also as risk markers on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61) and Day 90 Visit (Day 91) Blood glucose, TG, and TC from the safety laboratory panel evaluated also as risk markers on Day 0, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91).
- ^f Pre-study chest X-ray (with anterior-posterior and left lateral views) may have been used, if obtained within 6 months prior to Screening.
- ^g THS 2.2 Menthol product test was conducted as the last procedure of eligibility check on Day -2 (and after urine pregnancy test had been confirmed negative in female subjects to exclude pregnancy).
- ^h CO breath test; Days -1 to Day 5: the test was conducted 4 times per day. The first test was conducted within 15 minutes prior to the first product use (for subjects in the THS 2.2 Menthol and mCC arms) and between 08:00-09:30 AM for subjects in the SA arm. The other 3 tests were conducted as per [Section 9.5.1.1.2. Day -2, Day 6, Day 30 Visit \(Day 30\), Day 60 Visit \(Day 60\) and Day 90 Visit \(Day 90\)](#): once during the visit, irrespective of the time of product use.
- ⁱ COHb; assessments were performed in conjunction with CO breath tests, where applicable. Day -1 to Day 4: one blood sample in the evening between 08:00-09:30 PM. Day 5: one blood sample within 15 minutes prior to product use (for subjects in THS 2.2 Menthol and mCC arms) and between 08:00-9:30 AM for subjects in the SA arm. The other 3 tests were conducted as per [Section 9.5.1.1.2. Day 30 Visit \(Day 30\), Day 60 Visit \(Day 60\) and Day 90 Visit \(Day 90\)](#): one blood sample collected during the visit, irrespective of the time of product use.
- ^j Nicotine/cotinine; Day 0 to Day 4 (all study arms): one blood sample between 08:00-09:30 PM. Day 5 and Day 6 (THS 2.2 Menthol and mCC arms): one sample within 15 minutes prior to the product use; 8 blood samples after product use (T0), each at 2 hour intervals. On Day 6, 2 blood samples were drawn. The first sample was 20 hours after T0 and the second blood sample was 24 hours after T0 (with T0 being the time of the first product use on Day 5). Day 5 and Day 6 (SA arm): on Day 5, one blood sample in the evening between 08:00-09:30 PM on Day 5 and one blood sampling between 08:00-09:30 AM on Day 6. Day 30 Visit (Day 30), Day 60 Visit (Day 60), Day 90 Visit (Day 90) (all study arms): one blood sample drawn during the visit, irrespective of the time of product use.
- ^k Evaluated also as risk markers on Day 0, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91).
- ^l Evaluated also as risk marker on Day 0, Day 6, Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91).
- ^m Evaluated also as risk marker on Day 0, and Day 90 Visit (Day 91).



- ^a Evaluated also as risk markers on Day 0, Day 5, Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90).
- ^o Daily during Ambulatory Period only (from Discharge on Day 6 to Day 90 only). Use of any tobacco/nicotine containing products were captured in the e-diary.
- ^p QSU-brief: Daily, from Day -1 to Day 5 and at every visit during the Ambulatory Period, i.e., Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90).
- ^q MNWS daily from Day 0 to Day 6 prior product use but no later than 10:00 AM and at every visit during the Ambulatory Period no later than 10:00 AM, i.e., Day 30 Visit (Day 31), and Day 60 Visit (Day 61) irrespective of time of product use and on Day 90 Visit (Day 91) prior to smoking.
- ^r MCEQ: Day -1 to Day 5 on a daily basis, and on Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90). On Day -1 and Day 0, MCEQ was asked to all subjects. From Day 1, MCEQ was asked to THS 2.2 Menthol and mCC arms only.
- ^s On Day 0, HST assessment was performed in all subjects smoking mCC compatible with the HST SODIM[®] device. On Day 1, Day 4, Day 30 Visit, (Day 30) and Day 60 Visit (Day 60) and Day 90 Visit (Day 90), HST. Smoking topography with the HST device was not performed in subjects smoking mCC that were incompatible with the HST SODIM[®] device (e.g., slim mCC). No HST assessments were performed in subjects in the SA arm.
- ^t Cough questionnaire conducted daily from Day 0 to Day 6 prior product use but no later than 10:00 AM and at every visit during the Ambulatory Period no later than 10:00 AM, i.e., Day 30 Visit (Day 31), and Day 60 Visit (Day 61) irrespective of time of product use and Day 90 Visit (Day 91) prior to smoking.
- ^u Samples were only taken if additional consent for bio-banking was given by the subject.
- ^v Spontaneous reporting of new AEs/SAEs by the subject and active follow-up of ongoing AEs/SAEs by the site.

**Table 9 Schedule for 24-hour Urine Collection Assessments**

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

Abbreviations: Abbreviations: 8-epi-PGF_{2α} = 8-epi-prostaglandine F2 alpha; 11-DTX-B2 = 11-dehydro-thromboxane B2

^a MHBMA, 3-HPMA, S-PMA, Total NNAL, 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, 3-hydroxybenzo(a)pyrene, HMPMA, S-BMA, NEQ.

^b Samples were only taken if additional consent for BoExp bio-banking was given by the subject.

Note: During the Confinement and Ambulatory Periods, when the BoExp is mentioned to be assessed on Day x, it corresponds to the start of urine collection. For example, for NEQ assessed on Day 5, it was the measurement of NEQ in the Day 5 to Day 6 24-hour urine collection.



9.5.8 Appropriateness of Measurements

The laboratory measures used in this study were selected based on the following criteria:

- the availability of a validated analytical method;
- measure was known to be directly or indirectly affected by smoking;
- measure was readily reversible after smoking cessation;
- timeframe of reversibility of measure in the perspective of the study duration;
- practicality/acceptability by subjects; and
- robustness (rapid, simple, accurate).

All used questionnaires were either available as a questionnaire in the local language (SES, MNWS, and HST questionnaire) or were forward-translated and back-translated with subsequent independent verification.

9.6 Data Quality Assurance

Details of QC and quality assurance 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 agreed monitoring plan 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 permitted access to all medical records to the Monitor in order that entries in the CRFs could be verified. The Principal Investigator, as part of their responsibilities, was expected to ensure that the study adhered to GCP requirements.

9.6.1.1 Investigator Meeting

An Investigator’s meeting (IM) was held prior to the Site Initiation Visit (SIV). During this meeting, general training on 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

This study applied a split in the SIV process in several non-consecutive visit days to accommodate training of Laboratory Sample Handling Manual related to Covance (only for Seishukai Clinic) and delivery of the IP.



For the Seishukai Clinic a first pre-SIV visit occurred on the same date as the IM, followed by a second pre-SIV for training of Covance Laboratory Sample Handling Manual. Following the delivery of the IP and clinical supplies, the third and final part of SIV occurred. This meeting included, but was not limited to the following activities:

- Review of IP supplies, dispensation, storage, and accountability,
- Clinical supplies verification

These pre-SIV/IM and SIV, were performed by the CRA and/or the Project leader and covered all necessary trainings to site staff members before any recruitment process started.

At the Tokyo Heart Center a pre-SIV occurred with the IM followed by a SIV. At a later date, an SIV was performed by the CRA and covered all necessary trainings to site staff members before any recruitment process started and included but was not limited to the following activities:

- Review of IP supplies, dispensation, storage, and accountability,
- Clinical supplies verification

Additional SIVs occurred due to the enrollment of additional subjects at the Tokyo Heart Center following the discontinuation of the study at the Seishukai Clinic (See [Section 9.8.1](#)),

9.6.1.3 Routine Monitoring Visits

Communication by telephone, mail, and e-mail were used as needed to supplement site visits. The purpose of these visits was, but not limited, 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.

Site 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 Principal Investigator, or a designated member of the Principal Investigator's study collaborator, were available during monitoring visits 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 (b) (4) CRA was responsible for performing the close-out visit according to (b) (4) SOPs. The initial close-out visits took place on 19th November (Tokyo Heart Center) and 20th November (Seishukai Clinic) with final visits taking place on 26-Jan-2015 and 28-Jan-2015, respectively. These visits occurred after database lock, which occurred on 07 November 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 e-diaries, devices, and SODIM[®] devices, and butt collectors were 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, IP shipment and accountability logs.
- Review procedure for record retention, IRB notification, and publication rights with Principal Investigators.
- Advise site to notify the IRB of study closure, if applicable.

Confirmation and follow-up letters were sent to the site for all visits.

9.6.2 Training of Staff

At the Investigator meeting and SIV, training on the following activities was provided:

- 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 deviation.
- Training on use of IP and devices, IP supplies shipment/documentation.
- Training on HST, use of SODIM[®] device, and collection/shipment of tobacco plugs and filters procedure.
- Laboratory Manual/instructions- kits and labels- laboratory sample shipments.
- Presentation of safety reporting procedures- SAE form and SAE handling.
- Pregnancy reporting procedures- pregnancy form and pregnancy handling.
- Refreshed training on GCP requirements.



- IXRS[®] randomization procedure and training.
- Electronic data capture system training.
- ePRO system training.
- Review of site monitoring schedule and activities.

Several visits were needed to entirely train the site before considering site initiation effective (pre-initiation visits). If required, training was provided on an ongoing basis throughout the study.

In addition to the Investigator meeting, the Principal Investigators ensured that appropriate training relevant to the study was provided to all study collaborators involved, and that any new information relevant to the performance of this study was forwarded to them 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 the protocol ([Appendix 16.1.1](#)), and all Data Management activities were described in detail in the Data Management Plan 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 or authorized designee and then captured in the CRFs at the study site. The subject questionnaires and the VAS were entered by the subject directly in the ePRO device or on paper copy. Trained study personnel were responsible for capturing the data from the observations, tests, and assessments specified in the protocol in the source documents and then transferring the data into the CRF according to the CRF Completion Guidelines.

The Principal Investigators 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 must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject was checked against the source documents at the study site by the CRA. Instances of missing or unclear data were discussed with the Principal Investigators for resolution. An electronic CRF was generated for all subjects that signed the ICF.



A copy of the CRF, the subject questionnaires, smoking diaries, and VAS used in this study are provided in ([Appendix 16.1.2](#)). Further details on the collection of study data for this study are provided in 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. At the point of database lock, only the protocol deviations identified and recorded by the CRA had been reviewed and categorized by the Sponsor. Additional protocol deviations were programmatically identified and categorized during the data programming using pre-defined rules. Protocol deviations identified by the CRA and programmatically after database lock were used to exclude subjects with non-evaluable protocol deviations from the PP Set.

Further details on the recording of protocol deviations are provided in the protocol and notes to file ([Appendix 16.1.1](#)).

9.6.3.2 Data Handling

All study data were 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 Covance Data Management Team. The Data Management Team at Covance prepared a Data Management Plan, reviewed and approved by the Sponsor, prior to the start of the study. This document described, in detail, the Data Management-related procedures and processes.

All data of 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 is the property of the Sponsor irrespective of the location of the database and the Data Management CRO.

9.6.3.3 Data Validation

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

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

9.6.3.4 Coding

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



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

Adverse events: MedDRA, Version 16.0.

Medications: WHO - Drug Dictionary Enhanced (WHO-DDE) and Anatomical, Therapeutic, and 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 [5] terminology.

9.6.3.5 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/were declared soft-locked. Access to change data in the soft-locked database or to change selected data at this time was limited to specified Data Management personnel.

After data review by the Sponsor, resolution of all raised queries, and QC of the changed data, the database was declared locked on 07 November 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 conducted. 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 could have 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 data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. The Principal Investigator/head of investigational site designee contacted the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.



Sponsor requested discontinuation of the Seishukai Clinic due to failure of the site to meet sample collection procedures and data recording procedures as defined in the protocol and according to ICH-GCP guidance. Thus, the study at this site was terminated. (see [Appendices 16.1.7](#) and [16.1.1](#) for further details).

The Principal Investigators and study collaborator 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 Investigators understood 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 for this study 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 Statistical Analysis Software® (SAS®), Version 9.3 and Version 9.4.

9.7.1.2 Data Sets for Analysis

The PP Set population was the primary analysis set for BoExp and CREs. The Full Analysis Set (FAS) was the primary analysis set for compliance to randomization arm. Exposure and questionnaires were described by randomization arm and according to product use categories (see [Table 10](#)).

A sensitivity analysis was run on the Compliant Population for the BoExp and CREs.

Safety data were analyzed using the Safety Population and the Full Safety Population by randomization arm and according to product use categories (see [Table 10](#)).

9.7.1.2.1 Full Analysis Set

The FAS consisted of all the randomized subjects who had at least 1 post-randomization product use experience, if randomized to THS 2.2 Menthol or mCC, and had at least 1 valid non-safety assessment (THS 2.2 Menthol, mCC, and SA arms). Subjects that were enrolled at the site that terminated due to ICH/GCP non-compliance were excluded from the FAS (see [Section 9.6.4](#)).



9.7.1.2.2 Per Protocol Set

The PP Set was a subset of the FAS and included all randomized subjects who had no major protocol deviations impacting evaluability (as defined in Section 10.2 of the SAP [Appendix 16.1.8]).

The PP Set was assessed for each product use time period 1 to 4 (see Table 10), considering the product deviations occurring only during that period, independent of any exclusion from the population in previous periods.

Table 10 Stratification Labels for Product Use

Stratification Factor	Label (Definition)
Product Use Time Periods	Period 1 ([Day 1-Day 6 Confinement]) Period 2 ([Day 6 Ambulatory-Day 30 Visit]) Period 3 ([Day 30 Visit-Day 60 Visit]) Period 4 ([Day 60 Visit-Day 90 Visit])
Product Use Categories for mCC arm	CC Only (Exclusively CC) CC Dual (Use of other products)
Product Use Categories for SA arm	Abstinent Predominantly Abstinent Not Abstinent
General Product Use Categories for THS 2.2 Menthol arm	THS 2.2 [70-100%] Dual [30-70%] CC [0-30%]
Detailed Product Use Categories for THS 2.2 Menthol	Exclusively THS 2.2 (100%) Primarily THS 2.2 ([95-100]%) Predominantly THS 2.2 ([70-95]%) Dual Mostly THS 2.2 ([60-70]%) Dual Balanced ([40-60]%) Dual Mostly CC ([30-40]%) Predominantly CC ([15-30]%) Primarily CC ([0-5]%) Exclusively CC (0%)

Abbreviations: CC = conventional cigarette; mCC = Menthol conventional cigarette; SA = smoking abstinence; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol.

9.7.1.2.3 Safety Populations

Safety Population

Before randomization the Safety Population consisted of all the subjects who had at least 1 exposure to THS 2.2 Menthol (including the product test at Admission Day). This also



included any randomized subjects who had no valid safety assessment post-randomization.

After the randomization, the Safety Population included all randomized subjects who had at least 1 valid safety assessment post-randomization. Subjects in the safety populations were analyzed according to product use categories defined over the whole Ambulatory Period.

Although subjects that were enrolled at the site that was terminated due to ICH/GCP non-compliance were excluded from the Safety Population, they were listed within the Full Safety Population.

Full Safety Population

The Full Safety Population consisted of all the subjects who had at least 1 exposure to THS 2.2 Menthol (including the product test at Admission Day). Safety evaluation was presented before and after randomization for the Safety Population (see [Section 9.7.1.2.3](#)).

9.7.1.2.4 Compliant Population

The Compliant Population was a subset of the PP Set for subjects from the THS 2.2 Menthol arm who were exclusive THS 2.2 Menthol users, or for subjects from the mCC arm who were exclusive users of mCC, or for subjects in the SA arm who were abstinent (see Section 6.3.3 of the SAP [[Appendix 16.1.8](#)]).

9.7.1.3 Stratification

Each sex and each of the current mCC consumption levels over the last 4 weeks, as reported during Screening (10 to 19 mCC/day and > 19 mCC/day), had a quota applied to ensure they represented at least 40% of the total randomized study population. See [Section 9.4.6](#) for further details on the randomization lists.

9.7.1.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics were listed and summarized for the Safety Population, FAS, and PP Set in Periods 1 to 4. In addition, the data were summarized, stratified by sex and mCC consumption for the PP Set at Period 1 and 4.

The demographic variables age, sex, race, body weight, height, BMI, and waist circumference were summarized by randomization arm, and by the 2 stratification factors (sex, and mCC consumption), using the following descriptive statistics: number of subjects (n), number and percentage of subjects with missing data, arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum,



maximum, and number and/or counts and percentages within specified categories (see Section 12.1.3 of the SAP in [Appendix 16.1.8](#)).

No inferential analyses were conducted for the demographic and baseline characteristics.

9.7.1.4.1 Current Conventional Cigarette Brand Consumption

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

The following smoking characteristics at Admission (Day -2) were summarized and listed: ISO tar yields (continuous and categorized as 1 to 5 mg, 6 to 8 mg, 9 to 10 mg, and >10 mg), ISO nicotine level (continuous and categorized as ≤ 0.6 mg and > 0.6 mg), and number of mCCs smoked (categorized as 10-19 cig/day and >19 cig/day). The summaries were presented for the Safety Population, FAS, and PP Set.

9.7.1.4.2 Smoking History and Willingness to Quit Smoking

Smoking history, including whether subjects had smoked for at least the last 3 consecutive years and the subject’s mCCs consumption during the previous 4 weeks were listed by randomization arm at Screening and Admission (Day -2) where applicable.

9.7.1.4.3 Socio-economic Status Questionnaire

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

9.7.1.4.4 Measurement of Product Compliance

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

Levels of CO in exhaled breath were measured in the SA arm to ensure that the subjects had not smoked any cigarettes. This served as a compliance tool starting from Day 2,



because of possible carry over effect. These data (continuous and categorical) were summarized and listed by product use category in the SA arm.

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

9.7.1.4.5 Extent of Exposure

Details of the product test prior to enrollment and of product use after randomization were listed and summarized. During the Confinement Period the daily usage, as recorded in the log, was summarized by randomization arm.

The maximum and average daily usage of the assigned product and non-assigned product was summarized over the whole Ambulatory Period, as recorded by the subject, and for each of the Periods 2 to 4.

All summaries were produced for the Safety Population and for the PP Set at Periods 1 to 4. Summaries of data in the Ambulatory Period were also repeated for the FAS.

In addition the number and percentage of subjects falling into each product use category ([Section 9.4.12.1](#)) during the Ambulatory Period were tabulated.

The average product use data were also tabulated by randomized product and by product use categorization ([Section 9.4.12.1](#)).

9.7.1.4.6 Other Baseline Data

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

- Cotinine urine test.
- Urine pregnancy test.
- Chest X-ray.
- Urine drug screen.
- Serology (excluding HIV status).
- Alcohol breath test.
- Prior medication.
- Willingness to use THS 2.2 Menthol products.



- Product preference question.

Prior Medication was listed by product using preferred term (PT) and ATC codes (see [Section 9.6.3.4](#)). A flag was presented on the listing indicating whether the medication was prior or concomitant.

Product preference was collected at Admission (Day -2) and stated the product which the subject preferred were randomized to (THS 2.2 Menthol, mCC, SA, or no preference). Data was summarized by randomization arms along with baseline characteristics. Willingness and ability to use the product was included in the disposition summary table for all screened subjects.

9.7.1.5 Primary Analyses

9.7.1.5.1 Analysis of Biomarkers of Exposure for Primary Objectives

The BoExp included as endpoints in the primary objective and assessed for the comparison of THS 2.2 Menthol and mCC in a confinement setting were MHBMA, 3-HPMA, S-PMA (concentration adjusted for creatinine) in 24-hour urine, and COHb in blood (expressed as % saturation of hemoglobin), as measured on Day 5. The listing of the COHb data was flagged for whether a subject's COHb was <2%. The BoExp included as endpoints in the primary objective and assessed for the comparison of THS 2.2 Menthol and mCC in an ambulatory setting was Total NNAL (adjusted for creatinine) in 24-hour urine as measured at the Day 90 Visit.

The BoExp used for the primary analysis were summarized using descriptive statistics including the number of subjects (n), the number and percentage of subjects with missing data, the arithmetic mean, arithmetic SD, 95% confidence interval (CI), median, first and third quartiles, minimum, and maximum; for log-normal data the geometric mean, geometric 95% CI, and geometric coefficient of variance (CV) were also tabulated for each study arm. In addition, BoExp for the primary objective were summarized, stratified by sex and mCC consumption, for the PP Set at Period 1 and 4.

The endpoints included in the primary objectives were log-transformed (base_e) prior to analysis. The analysis compared (1) the evening COHb level (20:00-21:30) on Day 5, (2) urinary concentrations of MHBMA, 3-HPMA and S-PMA adjusted for creatinine on Day 5, and (3) urinary concentrations of Total NNAL adjusted for creatinine on Day 90 Visit between the THS 2.2 Menthol and mCC arms for the PP Set. An analysis of covariance (ANCOVA) [33] model was used with terms for the log-transformed baseline value, sex, average daily mCC consumption over the last 4 weeks as reported during Screening (stratification factors), and randomization arm.



The least squares (LS) means and estimate of the difference and the 95% CI were back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), two-sided 95% CI and one-sided p-value, were tabulated. THS 2.2 Menthol : mCC effects were graphed in a forest plot. Adjustment for multiple comparisons is described further in [Section 11.4.6](#).

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

The hypothesis that was tested for each BoExp of the primary objective endpoints was that the geometric mean level of the BoExp for THS 2.2 Menthol was lower relative to mCC. The hypothesis was tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and at the Day 90 Visit for Total NNAL.

9.7.1.5.2 Sensitivity Analysis

As a sensitivity analysis, the ANCOVA model described in [Section 9.7.1.5.1](#) was repeated for the PP Set data on Day 5 and Day 90 data by means of a mixed model approach, without the last observation carried forward (LOCF) data imputation described in Section 12.1.5 of the SAP ([Appendix 16.1.8](#)). Any data outside of the allowed time window (Table 18 of the SAP in [Appendix 16.1.8](#)) on Days 5 and 90 was excluded from the analysis.

An additional sensitivity analysis was produced for the primary analysis, summaries, and graphs of the COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL for the Compliant Population for THS 2.2 Menthol vs mCC. The analysis used the same model as described in [Section 9.7.1.5.1](#).

9.7.1.6 Secondary Analyses

The analyses of COHb, MHBMA, 3-HPMA, and S-PMA on Day 90 and Total NNAL on Day 5 were repeated for the PP Set.

The analyses of the COHb, MHBMA, 3-HPMA, S-PMA on Day 5/Day 90 and Total NNAL on Day 90 were repeated for the FAS as described in [Section 9.7.1.5.1](#). These endpoints were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as for the primary analysis for the PP Set. Urinary endpoints were analyzed using concentrations adjusted for creatinine.

The baseline for the biomarkers measured in urine was defined as the subject's last assessment prior to subject's first randomized product use in mCC/THS 2.2 Menthol arms. In the SA arm, the subject's last assessment was prior to 10:00 AM on Day 1.



9.7.1.6.1 Analysis of Biomarkers of Exposure for Secondary Objectives

The BoExp included as endpoints in the secondary objectives were exhaled CO and Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, and NEQ (all analyzed from a 24-hour urine collection) on Day 5 and Day 90 and were described as reported in [Section 9.7.1.5.1](#). Urine parameters were analyzed as concentration adjusted for creatinine and the quantity excreted in urine over 24 hours. In addition the quantity excreted in urine over 24 hours for MHBMA, 3-HPMA, S-PMA and Total NNAL was also presented as above.

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

Biomarkers of exposure were analyzed using the same model described in [Section 9.7.1.5.1](#). No adjustment was made for multiple comparisons. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the statistical significance was evaluated for the results of the analysis on Day 90 values. Least squares means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated. Forest plots of the ratios and 95% CI were also produced.

Biomarkers of exposure were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as above for the PP Set. In addition, the sensitivity analyses described in [Section 9.7.1.5.2](#) were repeated for the BoExp for secondary objectives.

9.7.1.6.2 Nicotine and Cotinine Concentrations

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

Nicotine and cotinine concentrations at each post-baseline time point were analyzed in the log space using an ANCOVA model with terms for log-transformed baseline concentration, stratification factors, and randomization arm. No adjustment was made for multiple comparisons. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated.

All figures, summaries, and analyses were performed using the PP Set and FAS by randomization arm.

9.7.1.6.3 Nicotine and Cotinine Pharmacokinetic Parameters

The nicotine and cotinine peak plasma concentration (C_{peak}) and time to peak concentration (t_{peak}) were obtained directly from the concentrations taken on Day 5. The



C_{avg} on Day 5 was calculated by dividing the area under the time-concentration curve from 0 to 24 hours ($AUC_{0-24\text{ h}}$) by 24, where the $AUC_{0-24\text{ h}}$ was calculated using the linear trapezoidal rule. Since the samples were taken while the subjects were smoking freely all samples must have been non-missing for the parameters to be calculated as C_{peak} (and t_{peak}) could have occurred at any time.

The analysis compared the log-transformed C_{peak} and C_{avg} on Day 5 between the THS 2.2 Menthol and mCC arms. An analysis of variance (ANOVA) model was used with terms for stratification factors and randomization arm. Least squares means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated.

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

All summaries and analyses were performed using the PP Set and FAS.

9.7.1.6.4 CYP1A2 Activity

Cytochrome P450 1A2 activity was calculated in plasma as the metabolic ratio of PX to CAF, both expressed in molar equivalent (nmol/L).

A conversion factor was applied as follows:

Paraxanthine: The molecular weight is 180.166 g/mol. Therefore, to convert PX in ng/mL to nmol/L, the result in ng/mL was multiplied by 5.550.

Caffeine: The molecular weight is 194.193 g/mol. Therefore, to convert CAF in ng/mL to nmol/L, the result in ng/mL was multiplied by 5.150.

Cytochrome P450 1A2 was measured in plasma on Day 0, Day 5, and Day 90. Descriptive statistics of the values and percent change on Day 5 and Day 90 from baseline and supportive listings were provided.

The analysis compared the log-transformed Day 5 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms. Analysis of covariance models were used on CYP1A2 activity levels with terms for log-transformed baseline stratification factors and randomization arm. No adjustment was made for multiple comparisons. If the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the statistical significance was repeated for the analysis on the Day 90 values. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated.



Cytochrome P450 1A2 activity was also examined to compare the observed reductions in THS 2.2 Menthol versus SA using the same methodology as above. If there were any CYP1A2 assessments performed within 5 half-lives since the use of a concomitant medication affecting CYP1A2 activity, the analysis was repeated by excluding these assessments for both the PP Set and FAS.

All summaries and analyses were performed using the FAS and PP Set.

9.7.1.6.5 Risk Markers

Details of the CREs are presented in [Section 9.5.1.2.1](#).

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

The analysis compared the results on Days 5, 30, 60, and 90, where applicable, between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms for the FAS and PP Set. An ANCOVA model was used with terms for baseline, stratification factors, and randomization arm. No adjustment was made for multiple comparisons.

Blood pressure, HbA1c, LDL cholesterol, HDL cholesterol, TG, TC, WBC, body weight, and waist circumference were analyzed in the regular scale. 8-epi-prostaglandin F2 α , 11-DTX-B2, sICAM-1 were analyzed in the logarithmic scale. If there was evidence of non-normality by means of Shapiro-Wilks test, glucose, hs-CRP, homocysteine, fibrinogen, and platelet count CREs were logarithmically transformed for analysis. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) or ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated along with a forest plot of the results.

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

All tables and analyses were produced for the FAS and PP Set. Figures were produced for the PP Set.

9.7.1.7 Exploratory Analysis

9.7.1.7.1 Questionnaires

Fagerström Test for Nicotine Dependence Questionnaire

The FTND used in its revised version [27], as updated in 2012 [28] was conducted at Screening and at the Day 90 Visit to determine the subject's dependence on nicotine. The questionnaire consisted of 6 questions, which subjects answered themselves.



Table 11 shows the 6 questions and the scores associated with each question.

Table 11 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, e.g. in church, at the library, cinema, etc.?	• Yes	1
	• No	0
3. Which cigarette would you hate most to give up?	• The first one in the morning	1
	• All others	0
4. How many cigarettes/day do you smoke?	• 10 or less	0
	• 11 to 20	1
	• 21 to 30	2
	• 31 or more	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 total 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 FTND total score, descriptive statistics, and frequency tables were categorized into the following categories:

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

The FTND score value and the number and percentage of subjects in each category (mild/moderate/severe) were tabulated for Screening and the Day 90 Visit. The percent change from baseline in the FTND score on Day 90 were also tabulated. The changes in the categories were also tabulated in a shift table. All summaries and shift tables were performed using the PP Set, FAS, and Compliant Population.

Questionnaire of Smoking Urges-Brief

Details of the QSU-brief [30] are presented in Section 9.5.6.5.4. The QSU-brief consists of 10 items as tabulated in Table 12.

Table 12 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 were 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 [30]. Each factor was a subset that included 5 of the 10 questions as defined in Table 12. 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 factors and total scores were calculated by averaging non-missing item scores if at least 50% were non-missing, otherwise the factor or total score was set to missing.

The change from baseline was calculated for the total score and the 2 factor scores (relief and reward). The total score and 2 factor scores, along with the percent change from baseline were summarized. The answers to the individual questions, along with the factor scores, total scores, changes and percent changes from baseline were listed. The profiles of the raw means from baseline to Day 90 Visit for the total score and 2 factor scores were produced.

The analysis was performed separately for each post-baseline time point in the factor and total scores. An ANCOVA model was used with terms for baseline QSU-BRIEF score, stratification factors, and randomization arm. No adjustment was made for multiple comparisons. Least squares means for each randomization arm along with the difference (THS 2.2 Menthol - mCC) and (THS 2.2 Menthol - SA) with 95% CI were tabulated.

All figures, summaries, and analyses were performed using the PP Set and the FAS.

*Modified Cigarette Evaluation Questionnaire*

Details of the MCEQ [29] are presented in [Section 9.5.6.5.3](#). The MCEQ consists of 12 items as tabulated in [Table 13](#).

Table 13 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 were 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% of the items within a subscale were non-missing, otherwise the subscale score was set to missing.

All summaries, profiles, and analysis were tabulated for the THS 2.2 Menthol and mCC only. The MCEQ was not captured for the SA arm.

The subscale scores, along with the percent change from baseline were summarized. The answers to the individual questions, along with the subscale scores, changes and percent changes from baseline were listed. The profiles of the raw means from baseline to Day 90 for the 5 subscale scores were produced.

The analysis was performed separately for each post-baseline time point in the subscales. An ANCOVA model was used with terms for baseline MCEQ score, stratification factors, and randomization arm. No adjustment was made for multiple comparisons. Least squares means for each product along with the difference (THS 2.2 Menthol – mCC) with 95% CI were tabulated.

All figures, summaries, and analyses were performed using the PP Set and the FAS.

*Minnesota Nicotine Withdrawal Questionnaire*

The MNWS [32] is a 24-hour recall that was completed by the subject him/herself daily from Day 0 to Day 6, and on the second day of every visit during the Ambulatory Period. From Day 0 to Day 6 only, the MNWS questionnaire was asked prior to start of product use/smoking and no later than 10:00 AM. On Day 31 and Day 61, the assessment of MNWS was conducted irrespective of the time of product use but no later than 10:00 AM, and on Day 91 the assessment of MNWS was conducted prior to smoking but no later than 10:00 AM.

The self-reported part of the MNWS consisted of the following 15 items which are rated over the last 24 hours on a scale of 0 to 4 (see Table 14). Higher scores indicated greater intensity on that scale.

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

**Table 14 Minnesota Nicotine Withdrawal Scale (Revised Edition)
Questionnaire Scores**

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

All summaries, profiles, and analysis were tabulated for the day before the assessment in the THS 2.2 Menthol, mCC, and SA arms.

The total score, along with the percent change from baseline were summarized. The answers to the individual questions, along with the total score, the change and percent



change from baseline were listed. The profiles of the raw means from baseline to Day 90 for the total score were plotted.

The analysis compared each post-baseline time point separately for the total score. An ANCOVA model was used with terms for baseline score, stratification factors, and randomization arm. No adjustment was made for multiple comparisons. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) and (THS 2.2 Menthol - SA) with 95% CI were tabulated.

All figures, summaries, and analyses were performed using the PP Set and the FAS.

Human Smoking Topography Questionnaire

The HST questionnaire was conducted on Day 0 for all subjects smoking mCC compatible with the HST SODIM[®] device, and on Days 4, 30, 60, and 90 for all subjects in the THS 2.2 Menthol and mCC arms, with the exception of mCC which were not compatible with the HST SODIM[®] device.

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

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

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

All summaries were performed using the FAS.

9.7.1.7.2 Human Smoking Topography Assessment

The HST SODIM[®] device measured and recorded the flow and other per-puff parameters listed below (Table 15) on Days 0, 1, 4, and the first day of each Ambulatory Visit. From the per-puff parameters, the per-cigarette parameters shown below were derived (representing average values or totals per-cigarette) (Table 16).

Prior to calculation of the per-cigarette parameters, the topography data were processed through analysis software. Only valid data for the per-cigarette parameters were part of the study database and analyzed.

The per-cigarette parameters derived from the HST assessments were averaged per day and summarized along with their changes from baseline. The per-puff and per-cigarette



parameters were listed. In addition the randomization arm mean and 95% CI per-cigarette parameters were presented graphically.

The averaged per-cigarette parameters were analyzed on Days 1, 4, 30, 60, and 90 separately using an ANCOVA model with terms for baseline score, stratification factors, and randomization arm. No adjustment was made for multiple comparisons.

Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) and 95% CI were tabulated.

All figures, summaries, and analyses were performed using the FAS and PP Set.

Table 15 Human Smoking Topography – Per-Puff Parameters

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

**Table 16 Human Smoking Topography – Per-cigarette Parameters**

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

9.7.1.7.3 CYP2A6 Activity

Cytochrome P450 2A6 activity was calculated in plasma as the metabolic ratio of trans-3' hydroxycotinine to cotinine, both expressed in molar equivalent (nmol/L) [26].

A conversion factor was applied as follows:

Cotinine: The molecular weight is 176.215 g/mol. Therefore to convert 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. Therefore to convert trans-3' hydroxycotinine from ng/mL to nmol/L the result in ng/mL was multiplied by 5.202.

Cytochrome P450 2A6 activity was measured in plasma on Day 0, Day 6, and Day 91. Descriptive statistics of the values, percent change on Days 6 and 91 from baseline, and supportive listings were provided. If either of the cotinine or trans-3'hydroxycotinine concentration were below the limit of quantification (BLOQ) then the ratio was not calculated.



The analysis compared the log-transformed Day 6 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms. Analysis of covariance models were used with terms for log-transformed baseline, stratification factors, and study arm. No adjustment was made for multiple comparisons. If the results from the Day 6 analysis were significant (one-sided p-value ≤ 0.025) then the statistical significance was repeated for the analysis on the Day 91 values. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated.

Cytochrome P450 2A6 activity was also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as above.

As there were a number of CYP2A6 assessments performed within 5 half-lives since the use of a concomitant medication affecting CYP2A6 activity, the analysis was repeated by excluding these assessments for both the PP Set and FAS.

All summaries and analyses were performed using the FAS and PP Set.

9.7.1.7.4 Relationship Between Biomarkers of Exposure and Nicotine Equivalents

The analysis of the relationship between NEQ and BoExp of the primary and secondary objectives was reported in a separate report as stated in [Section 9.8.2](#).

9.7.1.7.5 Relationship Between Risk Markers and Nicotine Equivalents

The analysis of the relationship between CREs and NEQ was reported in a separate report as stated in [Section 9.8.2](#).

9.7.1.7.6 Ames Mutagenicity Test

The 24-hour urine collection for the Ames mutagenicity test was on Day 0, Day 5, and Day 90. Descriptive statistics of the values and percent change on Day 5 and Day 90 from baseline of the YG1024+S9 mutagenicity were provided, along with listings.

All summaries were performed using the FAS and PP Set.

9.7.1.7.7 Visual Inspection of the Tobacco Plugs

The collection of the tobacco plugs from the THS 2.2 Menthol products was performed on Days 1 to 5, and Days 30, 60 and 90. The number and percentage of tobacco plugs showing each of the following criteria were summarized by day: “No overheating”, “White spot(s) inside the tobacco plug”, “Ashes inside the tobacco plug and burnt”, and “Missing”.

All summaries were performed using the FAS only.



9.7.1.7.8 Filter Analysis

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

9.7.1.7.9 Product Preference Analysis

The product preference as asked at Admission served as a sensitivity analysis for the product exposure.

All summaries were produced for the FAS. These data were also tabulated separately by product preference and by product use categorization during Periods 2-4 (see [Section 9.7.1.2](#)).

9.7.2 Post-hoc Analyses

Any post-hoc and additional exploratory analyses completed to support the 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 9.5.2](#).

The primary analysis of safety variables were conducted on the Safety Population using descriptive statistics.

9.7.3.1 Adverse Events

A product emergent AE was defined as an AE that occurred after first product use or that was present prior to first product use and became more severe after first product use. All other AEs were not summarized but provided in listings only.

All AEs occurring from the signing of informed consent were recorded electronically. However, only product emergent AEs were summarized. 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).

In general, AE summary tables reporting the number of events and the number and percentage of subjects reporting at least 1 AE was produced by study arm for the pre-randomization and randomized periods, as reported in [Section 9.7.3](#). Adverse event data during the randomized period was tabulated stratified by Confinement, Ambulatory, and safety follow-up.



Ambulatory AE data were reported by product use category (see [Table 10](#)) defined on product use over the whole Ambulatory Period. In particular, the general product use categories for THS 2.2 were used, and the [Predominantly Abstinence] and [Smoking Abstinence] categories were tabulated for THS 2.2 Menthol and mCC arm if at least 1 subject was associated to these categories.

9.7.3.1.1 All Adverse Events

A general summary table of AEs was tabulated 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) and expectedness (expected for THS 2.2 Menthol/mCC).
- The number of events and the number and percentage of subjects reporting at least 1 AE broken down by severity including each subject only once with his/her worst severity.
- The number of events and the number and percentage of subjects reporting at least 1 SAE.
- 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 (product use interrupted, product use reduced, product use stopped, not applicable, none), treatment given (yes, no), study discontinuation, other action taken.
- The number of events and the number and percentage of subjects reporting at least 1 AE related to study procedure.

Additional summary tables of AEs were tabulated 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 PT coded according to the MedDRA dictionary (Version 16.0).

If a subject had more than 1 occurrence of the same AE, the subject was counted only once within a PT with the worst occurrence based on the presentation (e.g., for presentation by severity = most severe, for presentation by relationship = most related). Missing information on the intensity of AE was counted as severe.

9.7.3.1.2 Serious Adverse Events (Including Deaths)

A summary table of SAEs was tabulated using the same approach as for AEs (see [Section 9.7.3.1](#)), and including the number of events and the number and percentage of subjects reporting at least 1 SAE, broken down by seriousness criteria (fatal, life-threatening, requires hospitalization, results in disability/incapacity, congenital anomaly/birth defect).



SAEs were also listed in separate listings by product.

9.7.3.1.3 Adverse Events Leading to Discontinuation

Summaries were tabulated for AEs leading to withdrawal, by product, as described in [Section 9.7.3.1](#). AEs leading to withdrawal were also listed in separate listings by product.

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 as concomitant.

All medications were listed by product using PT and ATC codes (WHO-DDE Q1 2013). A flag was presented on the listing indicating whether the medication was prior or concomitant.

Prior and concomitant medications were listed by randomization arm. Prior and concomitant medications were summarized by randomization arm for the Safety Population showing the number and percent of subjects who used the medication at least once by ATC first and second levels and preferred drug name.

9.7.3.3 Laboratory Safety Parameters

[Table 6](#) lists the hematology, clinical chemistry, and urine analysis parameters assessed in the study.

Any clinical safety laboratory test result that was outside of the normal reference range was reviewed by the Principal Investigator and assessed for clinical relevance. 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 values. These CTCAE grades were derived programmatically in the creation of the datasets. If the Principal Investigator considered the abnormal result to be of clinical relevance, then it was recorded as a concomitant disease at Screening, or if not present at Screening, as an AE during the study. If the condition worsens from Screening to after product use it was recorded as an AE.

The shift in toxicity grades from baseline to worst grade recorded while in the randomized period was tabulated for the clinical chemistry, hematology, and urinalysis parameters. Laboratory data were summarized and listed at Screening and Day 0 for the pre-Randomization period and at baseline, Day of Discharge (Day 6), Day 30 Visit, Day 60 Visit, and Day 90 Visit for the randomized period data together with changes from baseline. The number and percentage of subjects with normal results, high/low



results and abnormal clinical significant result (as defined by Principal Investigator comment), and CTCAE toxicity grading was tabulated for laboratory parameters, together with shift in normality (normal, abnormal non-clinically significant, abnormal clinically significant) and in CTCAE toxicity grading from baseline.

Listings for the clinical laboratory data included the following information: change from baseline, normal/high/low (with respect to the reference range), abnormal clinically significant (as defined by the Principal Investigator comments) and shift from baseline, the Principal Investigator comments, CTCAE grade and the shift in CTCAE grade. Only CTCAE grades greater than zero were tabulated.

9.7.3.4 Physical Examination

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

Body weight, waist circumference (recorded at Admission, Day of Discharge from Confinement [Day 6], Day 30 Visit, Day 60 Visit, and Day 90 Visit), and body height (recorded at the Screening Visit) were also listed together with BMI. Descriptive statistics of body weight, waist circumference, body height, and BMI, at baseline, Day of Discharge, and Day 90 Visit were tabulated for the Safety Population.

Summaries were tabulated for the Safety Population by study arm.

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

Details of the vital signs assessments and timings are provided in [Section 9.5.2.3](#). Systolic and diastolic blood pressure, pulse rate, and respiratory rate measured during the study were listed by study visit, including low/normal/high results.

Descriptive statistics were tabulated for supine systolic and supine diastolic blood pressure, pulse rate, and respiratory rate at baseline, and on every subsequent day of both the Confinement and Ambulatory Periods by product for each study day. Vital signs data were summarized together with changes from baseline.



9.7.3.6 Electrocardiogram

Details of the ECG assessments and timings are provided in [Section 9.5.2.5](#). Electrocardiogram data values and normality evaluations were listed by product and study day (Screening, Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit) together with changes from baseline and shift in normality. Electrocardiogram data from subjects, which had significant clinical findings, were highlighted in listings.

Descriptive statistics were tabulated for ECG data at baseline, and Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit by study arm. Electrocardiogram data were summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal non-clinically significant/abnormal clinically significant results.

9.7.3.7 Spirometry

The assessed spirometry parameters included:

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

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

Spirometry predicted values were standardized to the predicted set from the Japanese Respiratory Society. Spirometry data values and normality evaluation were listed by randomization arm and study day. Assessments performed after baseline (Day 0) were listed together with percent change from baseline and shift in normality. Spirometry data from subjects who had significant clinical findings were highlighted in the listings.

Descriptive statistics were tabulated for FEV₁ (L), FEV₁ (% pred), FVC (L), FVC (% pred), and FEV₁/FVC at baseline (pre or without bronchodilator), Day of Discharge (Day 6), and Day of Discharge (Day 91) by study arm, and overall for the Safety Population in the randomized period. Spirometry data were summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal non-clinically significant/abnormal clinically significant results. Data



with and without bronchodilator at Screening were summarized together with the spirometry data on Day 0 for the Safety Population in the pre-randomization period.

9.7.3.8 Medical and Surgical History

Medical history was defined as any condition that started and ended prior to Screening. Concomitant disease is defined as any condition that was ongoing at Screening. Medical history and concomitant diseases were coded using MedDRA (Version 16.0) and listed separately by randomization arm, SOC and PT. Medical History was also summarized by randomization arm, SOC, and PT for the Safety Population.

Concomitant diseases were summarized by randomization arm, SOC, and PT for the Safety Population.

9.7.3.9 Assessment of Cough

Details of the cough assessment and timings of assessment are provided in [Section 9.5.6.5.2](#).

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

9.7.3.10 Device Malfunction or Misuse

All events relating to the device type were listed for each subject, including event description, device type the event related to, severity of event, AE relationship, proposed solution, and onset/stop dates/times. Device events were classified according to the FDA Center for Devices and Radiological Health C54451 Medical Device Problem Codes [5] terminology.

A summary table of device events was tabulated by product, 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.

Device events and inventory were listed by product.

9.7.3.11 Product Compliance

Product compliance was ensured as described in [Section 9.4.12](#) and measured as described in [Section 9.7.1.4.4](#).

9.7.3.12 Extent of Exposure (Product Consumption)

Extent of exposure was determined as described in [Section 9.7.1.4.5](#).

9.7.3.13 Interim Analyses

No interim analyses were planned or conducted for this study.

9.7.4 Determination of Sample Size

Section 12.2 of the Protocol ([Appendix 16.1.1](#)) and Section 8 of the SAP ([Appendix 16.1.8](#)) discussed the ability to demonstrate on Day 5 a reduction of at least 50% on 4 selected BoExp for the primary objective endpoints and on Day 90 on a fifth BoExp for the primary objective endpoints in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

[Table 17](#) describes the expected CV and mean ratios between THS 2.2 Menthol and the 2 control arms in COHb, 3-HPMA, MHBMA, and S-PMA on Day 5 based on data from the PMI YVD-CS01-EU [\[10\]](#) (ClinicalTrials.gov: ID: NCT00812279) and PMI ZRHX-EX-01 [\[34\]](#) (ClinicalTrials.gov: ID: NCT01780714) studies. The mean ratios and CVs for the PMI YVD-CS01-EU [\[10\]](#) study were expected to be the same as THS 2.2 Menthol/mCC.

**Table 17 Coefficients of Variation**

BoExp	YVD-CS01-EU Study		ZRHX-EX-01 Study
	THS 2.2 / CC Mean Ratio (CV)	THS 2.2 / SA Mean Ratio (CV)	THS 2.2 Menthol / mCC Mean Ratio (CV)
COHb	0.40 (0.32)	2.10 (0.20)	0.44 (0.14)
3-HPMA	0.30 (0.50)	1.70 (0.33)	0.28 (0.20)
MHBMA	0.15 (0.70)	1.00 (0.35)	0.11 (0.47)
S-PMA	0.20 (0.70)	1.15 (0.42)	0.07 (0.50)

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CC = conventional cigarettes; COHb = carboxyhemoglobin; CV = coefficient of variation; mCC = menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS 2.2 = Tobacco Heating System 2.2.

Based on data from PMI ZRHX-EX-01 [34], a PMI-sponsored randomized, controlled, switching, open-label, parallel group, single-center study in 90 male and female adult smokers evaluating 6 biomarkers of tobacco smoke exposure over a 12-week period [35], the mean ratio and expected CV between THS 2.2 Menthol and the mCC control arm on Day 90 for Total NNAL was 0.30 and 0.60, respectively.

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

Table 18 describes the expected power to demonstrate a reduction on all 5 BoExp for the primary objective endpoints in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability using the assumptions from the PMI YVD-CS01-EU [10] (ClinicalTrials.gov: ID: NCT00812279) and PMI ZRHX-EX-01 [34] studies (ClinicalTrials.gov: ID: NCT01780714) sponsored by PMI given a sample size of 160 smokers (~80 in THS 2.2 Menthol, ~40 in mCC, and ~40 in the SA arm).

Table 18 Expected Power (YVD-CS01-EU and ZRHX-EX-01 Studies Assumptions)

Assumptions	Reduction					
	50%	51%	52%	53%	54%	55%
YVD-CS01-EU	94%	88%	81%	70%	56%	38%



ZRHX-EX-01	98%	97%	92%	76%	41%	6%
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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 (Version 3.0) dated 07 April 2014. This contained an amendment from Version 1.0 of the protocol (dated 26 June 2013) and an amendment from Version 2.0 of the protocol (dated 19 November 2013).

Version 1.0 of the protocol was amended to reflect the discontinuation of the study by the Sponsor at the Seishukai Clinic in response to audit findings conducted on 24 to 25 September 2013 by (b) (4) quality assurance. The subjects enrolled at this site were discontinued for non-compliance with ICH/GCP and were not included in the primary study population. To complete the study, enrollment was extended at the Tokyo Heart Center site to meet sample size requirements. Additional clarifications to Version 1.0 of the protocol were also included in the amendment.

Version 2.0 of the protocol was amended to update the name of the (b) (4) (b) (4) participating laboratory and add a new medical writer at PMI.

9.8.2 Changes in the Planned Analyses

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

- The analysis methodology and results of the second exploratory objective are reported in a separate report: To evaluate in smokers switching from mCC to THS 2.2 Menthol, and smokers continuing smoking mCC the relationship between NEQ and:
 - BoExp for primary and secondary objectives
 - Selected CREs and NEQ
- Serology for HIV 1/2 could not be transferred because of privacy laws; therefore this endpoint was not tabulated in the listings.
- Initially, the protocol stated that the PMI and Covance study statisticians were unblinded after finalization of the SAP; however, this was changed in the SAP to state that PMI and Covance study statisticians were unblinded after finalization of the SAP or database lock, whichever was later.
- The PMI study scientist was unblinded for the data review meeting; therefore the role of blinded reviewer was delegated.



- Listing and summaries of spirometry predicted values were tabulated standardized to the predicted set from the Japanese Respiratory Society, as measured by the spirometry devices.
- The product use categories ([Section 9.4.12](#)) were updated during the study. The [95-100]% category was renamed “Primarily THS 2.2” and a new category for 100% product use was named “Exclusively THS 2.2”. In addition, the [0-5[% THS 2.2 category was renamed “Primarily CC” and a new category for 0% product use was named “Exclusively CC”.

The following changes to the analyses planned in the SAP were made after the database locked:

- Listing 15.3.8.5 was removed from the planned SAP tables, figures, and listings (TFL) shells as it was not mentioned in the SAP and was a typographical error from a previous version of TFLs.
- The FTND summary was amended to include change from baseline instead of percent change from baseline as this analysis would be easier to interpret.
- Summary tables were not produced for the Full Safety Population, as they were not needed for safety interpretation.
- The numbering of various TFLs had changed from the SAP.
- FEV₁ was not planned to be analyzed as a CRE in the protocol, and therefore, a posthoc analysis was performed for FEV₁ following the same approach as for other CREs ([Appendix 15, Table 15.2.4.25.1.2](#)).
- The HST parameters were summarized and analyzed by PP Set by randomization arm and not on the FAS by product use categories. An additional geometric means analysis on the PP Set was conducted to facilitate the comparison with other studies ([Appendix 15, Tables 15.2.4.42.1 and 15.2.4.43.1](#), and [Figure 15.1.2.10.1](#)).
- The CREs were analyzed for all available assessments and not only on Day 90 as specified in the SAP.

There are a number of minor errors in TFL formatting and/or presented analyses in the TFLs. Due to the minor nature of these errors they have not been corrected in the TFLs, but have been correctly presented in this CSR or not reported in the CSR:

- Overall Ambulatory Period was calculated for [Table 15.2.2.3.1](#); however, due to different subjects present in different periods of the PP Set this is not accurate and should not be reported.



- The footnote of a number of figures ([Appendix 15, Figures 15.1.1.2 to 15.1.1.4, 15.1.2.1.1 to 15.1.2.10.1](#)) state that the last assessment prior to 06:29 AM on Day 1 in the SA arm was the baseline assessment; however, this is incorrect as it was actually prior to 10:00 AM.
- [Listing 15.3.3.1](#) contains all individual data for all urinary biomarkers assessed; however, the formatting of this listing is incorrect in the following way:
 - The listing should be 1 table; however, the page numbers are not continuous and instead start and end for each biomarker presented. In addition, the page numbering for each biomarker starts at page 2. For example, 1-NA has page numbers of 2 to 591; 2-NA has a page number of 2 to 613.
- [Table 15.2.4.30.1](#) has incorrect page numbering; however, PMI have confirmed no pages are missing.
- [Table 15.2.4.43](#) incorrectly states that the geometric LS means were calculated for the analysis of HST parameters; whereas it is actually the LS means that were calculated.
- The footnote of [Listing 15.3.6.11](#) states the questions for the FTND questionnaire items slightly differently to that of the questionnaire given to the subject, which is presented in [Appendix 16.1.2](#).



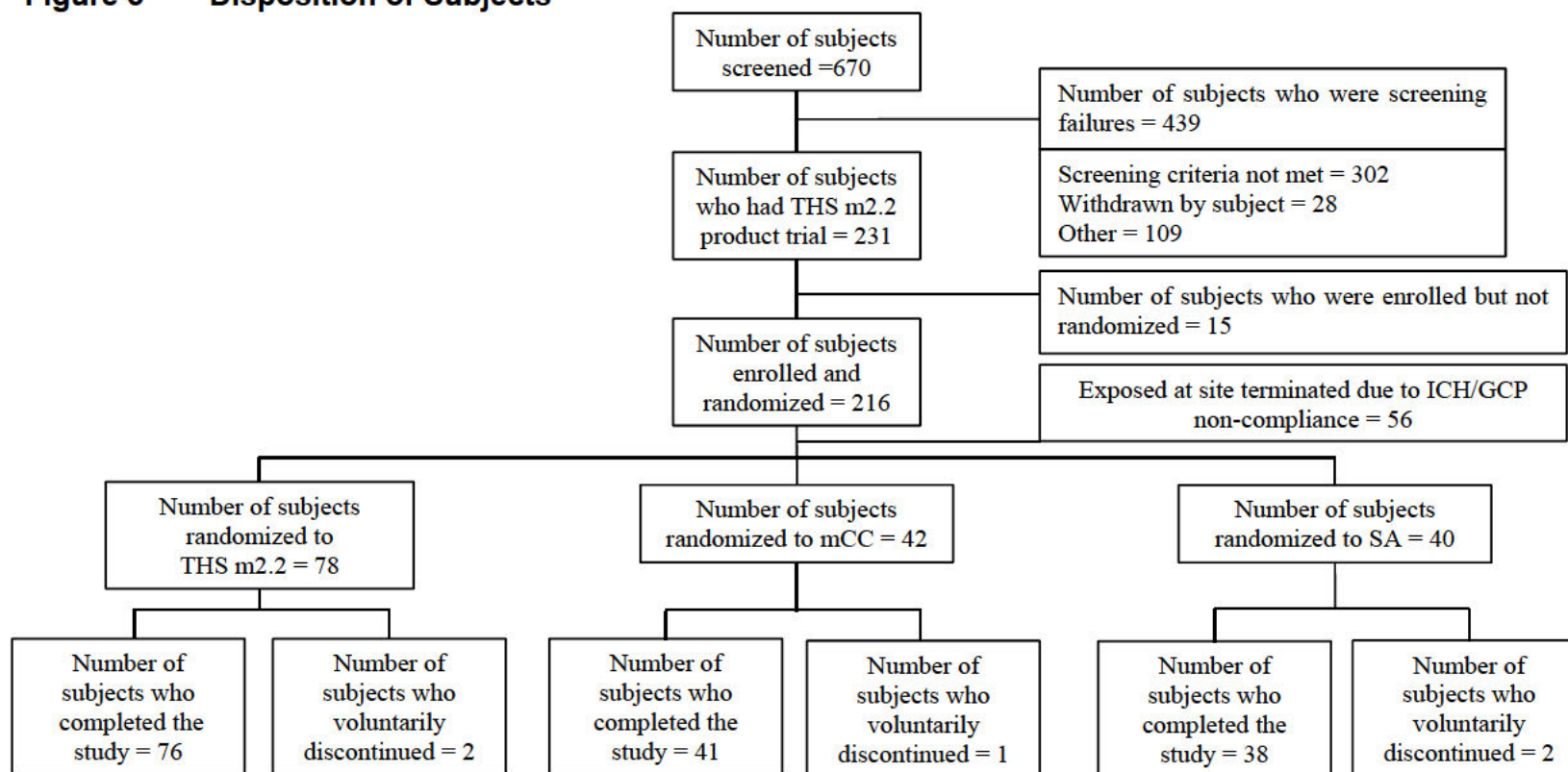
10 STUDY SUBJECTS

10.1 Disposition of Subjects

Subject disposition data are listed by subject in [Appendix 15, Listing 15.3.1.8](#).

Subject disposition data are summarized in [Appendix 15, Table 15.2.1.1](#) (disposition of subjects), [Table 15.2.1.2](#) (reasons for discontinuations), and shown in [Figure 3](#).

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

**Figure 3 Disposition of Subjects**

Abbreviations: mCC = Menthol conventional cigarette; SA = smoking abstinence; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Table 15.2.1.1](#) and [15.2.1.2](#)



Of the 670 subjects screened, 439 were screening failures and 231 went on to try the THS 2.2 Menthol product during the product trial. Of the 231 subjects who tried the THS 2.2 Menthol product, 15 subjects were discontinued from enrollment and not randomized; but completed the safety follow-up. Two of these 15 subjects were discontinued due to AEs ([Appendix 15, Listing 15.3.6.1.3](#)).

A total of 216 subjects were randomized. Of the 216 subjects randomized, 107 subjects were randomized to the THS 2.2 Menthol arm, 55 subjects were randomized to the mCC arm, and 54 subjects were randomized to the SA arm.

At the Seishukai Clinic, 1 subject was discontinued in Period 2 due to meeting an exclusion criterion and 55 subjects were discontinued from the study in Period 3 due to ICH/GCP non-compliance at this site ([Section 9.6.4](#)). All 56 subjects enrolled at this site were discontinued and were not included in the FAS or Safety Population. Therefore, the total number of subjects in the FAS was 160, with 78 subjects randomized to the THS 2.2 Menthol arm, 42 subjects randomized to the mCC arm, and 40 subjects randomized to the SA arm ([Appendix 15, Table 15.2.1.1](#)).

Overall in the FAS, 155 subjects completed all 4 periods of the study, with 2 subjects in the THS 2.2 Menthol arm, 1 subject in the mCC arm, and 2 subjects in the SA arm voluntarily discontinuing from the study ([Table 19](#)).

Table 19 Subject Discontinuations - FAS

	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)	Overall FAS (N=160)
Total number of discontinuations	2 (2.6%)	1 (2.4%)	2 (5.0%)	5 (3.1%)
Reason for discontinuation				
Adverse events – n (%)	0	0	0	0
Protocol violation – n (%)	0	0	0	0
Withdrawal by subject – n (%)	2 (2.6%)	1 (2.4%)	2 (5.0%)	5 (3.1%)
Lost to follow-up – n (%)	0	0	0	0
Other – n (%)	0	0	0	0

Abbreviations: FAS = Full Analysis Set; mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

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

Of those subjects in the FAS that discontinued, in the THS 2.2 Menthol arm, 1 subject voluntarily withdrew in Period 1, and 1 subject voluntarily withdrew in Period 4; in the mCC arm, 1 subject voluntarily withdrew in Period 1; and in the SA arm, 1 subject voluntarily withdrew in Period 1, and 1 subject voluntarily withdrew in Period 3 ([Appendix 15, Table 15.2.1.2](#)).



10.2 Protocol Deviations

Protocol deviations are listed in [Appendix 15, Listing 15.3.1.10](#).

The number and percentage of subjects with major and minor protocol deviations in the overall Safety Population (post-randomization) are summarized in [Appendix 15, Table 15.2.1.3.1](#) and shown in [Table 20](#).

Table 20 Protocol Deviations – Safety Population

	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)	Overall Safety (N=160)
Number (%) of subjects with:				
Major protocol deviations	12 (15.4%)	0	3 (7.5%)	15 (9.4%)
With evaluability impact	11 (14.1%)	0	3 (7.5%)	14 (8.8%)
Mis-randomization	1 (1.3%)	0	0	1 (0.6%)
Misuse of product in period 1	1 (1.3%)	0	1 (2.5%)	2 (1.3%)
Misuse of product in period 2	2 (2.6%)	0	0	2 (1.3%)
Misuse of product in period 3	5 (6.4%)	0	1 (2.5%)	6 (3.8%)
Misuse of product in period 4	6 (7.7%)	0	1 (2.5%)	7 (4.4%)
Without evaluability impact	3 (3.8%)	0	0	3 (1.9%)
Assessment missing	3 (3.8%)	0	0	3 (1.9%)
Violation	1 (1.3%)	0	0	1 (0.6%)
Minor protocol deviations	77 (98.7%)	42 (100%)	40 (100%)	159 (99.4%)
Procedure violation	24 (30.8%)	22 (52.4%)	19 (47.5%)	65 (40.6%)
Concomitant medication	4 (5.1%)	1 (2.4%)	2 (5.0%)	7 (4.4%)
Assessment missing	23 (29.5%)	10 (23.8%)	9 (22.5%)	42 (26.3%)
Time schedule deviation	64 (82.1%)	33 (78.6%)	28 (70.0%)	125 (78.1%)
Time missing	2 (2.6%)	1 (2.4%)	0	3 (1.9%)

Abbreviations: mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.1.3.1](#).

Major protocol deviations which were assessed to impact study evaluations included mis-randomization and misuse of the product. Major protocol deviations which were assessed not to have an impact on study evaluations included missing assessments and violations. Minor protocol deviations relating to procedure violations, concomitant medication, missing assessments or times, or time schedule deviations were reported. The majority of the minor protocol deviations were related to time schedule deviations.



10.3 Data Sets Analyzed

The number of subjects enrolled, randomized, and in each study arm are summarized in [Table 21](#).



Table 21 Summary of Analysis Population Sets and Reasons for Exclusions from Analyses

Population Sets	THS m2.2 n (%)	mCC n (%)	SA n (%)	Screen Failure n	Enrolled but not randomized ²	Overall n (%)
Screened	107	55	54	439	15	670
Full Safety Population	107	55	54	0	15	231
Subjects excluded	0	0	0	439	0	439
Not exposed to THS m2.2	0	0	0	439	0	439
Safety Population	78	42	40	0	15	175
Subjects excluded	29	13	14	439	0	495
Exposed at site terminated due to ICH/GCP non-compliance	29	13	14	0	0	56
Not exposed to THS m2.2	0	0	0	439	0	439
Total Subjects Randomized¹	107	55	54	NA	NA	216
Randomized subjects included in Full Safety Population (post-randomization)	107 (100)	55 (100)	54 (100)	NA	NA	216 (100)
Safety Population (post-randomization)	78 (72.9)	42 (76.4)	40 (74.1)			160 (74.1)
FAS	78 (72.9)	42 (76.4)	40 (74.1)			160 (74.1)
PP Set						
Period 1	76 (71.0)	42 (76.4)	39 (72.2)			157 (72.7)
Period 2	74 (69.2)	41 (74.5)	39 (72.2)			154 (71.3)
Period 3	71 (66.4)	41 (74.5)	38 (70.4)			150 (69.4)
Period 4	70 (65.4)	41 (74.5)	37 (68.5)			148 (68.5)
Compliant Population						
Period 1	76 (71.0)	42 (76.4)	39 (72.2)			157 (72.7)
Period 2	63 (58.9)	41 (74.5)	38 (70.4)			142 (65.7)
Period 3	65 (60.7)	41 (74.5)	38 (70.4)			144 (66.7)
Period 4	65 (60.7)	41 (74.5)	37 (68.5)			143 (66.2)

Abbreviations: GCP = Good Clinical Practice; ICH = International Conference on Harmonisation; mCC = menthol conventional cigarettes; NA = not applicable; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Note: Percentages appearing after randomization are based on the number of randomized subjects in each column.

[1]: "Total Subjects Randomized" refers to randomized subjects and not excluded due to ICH/GCP non-compliance.

[2]: Subjects were enrolled and had a product test; therefore, were exposed to THS m2.2. However, they were discontinued prior to randomization.

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

Data Source: [Appendix 15, Table 15.2.1.3.2](#) and [Table 15.2.1.1](#)



The total number of subjects randomized was 216; which excluded 15 subjects of the Full Safety Population (N=231) who tested the product but were not randomized to a study arm. Therefore, the Safety Population following randomization was 160 subjects, which excluded the 56 subjects who were exposed at the site which was terminated due to ICH/GCP non-compliance.

The FAS (N=160) was the same as the Safety Population following randomization. The number of subjects in each study arm of these populations was 78 subjects in the THS 2.2 Menthol arm, 42 in the mCC arm, and 40 in the SA arm.

Within the PP Sets, 1 subject in the THS 2.2 Menthol arm was excluded from all periods because he was mis-randomized; in addition, in Period 1, 2 subjects (1 subject in the THS 2.2 Menthol arm and 1 subject in the SA arm) were excluded because they were considered to be non-compliant to the randomized product after withdrawing from the study; in Period 2, 2 subjects in the THS 2.2 Menthol arm were excluded because they had protocol deviations for misuse of product and 1 subject in the THS 2.2 Menthol arm and 1 subject in the mCC arm discontinued at the end of Period 1; in Period 3, 5 subjects in the THS 2.2 Menthol arm and 1 subject in the SA arm were excluded because of protocol deviations of misuse of the randomized products, and 1 subject in both arms were discontinued in a previous period; in Period 4, 6 subjects in the THS 2.2 Menthol arm and 1 subject in the SA arm were excluded because of protocol deviations of misuse of the randomized products and 1 subject in the THS 2.2 Menthol arm and 2 subjects in the SA arm were discontinued in a previous period ([Table 20](#) and [Table 21](#)).

The Compliant Population was the same as the PP Set during the Confinement Period (PP Period 1) for all study arms, but was reduced in the PP Sets during the Ambulatory Period (Periods 2 to 4; [Table 21](#)) for the THS 2.2 Menthol arm due to product use and compliance data.

Within this report, the safety endpoints analyzed using the Safety Population pre- and post-randomization (175 and 160 subjects, respectively) were presented, compliance and product use data analyzed using the FAS were presented, and the biomarkers endpoints analyzed using the PP Set and Compliant Population were presented.

The number of subjects in the overall Safety Population and FAS, and in each study arm of the FAS, are summarized by the stratification factors in [Table 22](#).

**Table 22 Summary of Analysis Populations by Stratification Factors and Product**

Strata	FAS (N=160)			FAS (N=160)	Overall Safety (N=175)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)		
Sex					
Male, n (%)	45 (57.7)	25 (59.5)	22 (55.0)	92 (57.5)	102 (58.3)
Female, n (%)	33 (42.3)	17 (40.5)	18 (45.0)	68 (42.5)	73 (41.7)
Daily mCC consumption at Screening					
10 to 19 cig/day, n (%)	40 (51.3)	23 (54.8)	21 (52.5)	84 (52.5)	93 (53.1)
>19 cig/day, n (%)	38 (48.7)	19 (45.2)	19 (47.5)	76 (47.5)	82 (46.9)

Abbreviations: cig = cigarette; FAS = Full Analysis Set; mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2 Menthol.

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

The distribution of daily mCC consumption of 10 to 19 and >19 cigarettes/day was similar between the THS 2.2 Menthol, mCC, and SA arms in the FAS (and in the PP Set Periods 1 to 4). The distribution of male and female subjects showed a larger number of male subjects compared to female subjects for the overall Safety Population and each of the study arms in the FAS.

10.4 Demographics and Other Baseline Characteristics

10.4.1 Demographics

Subject demographic data are listed in [Appendix 15, Listing 15.3.1.7](#) and are summarized along with baseline characteristics data for the Safety Population, FAS, and PP Set in [Appendix 15, Table 15.2.1.4.1, Table 15.2.1.4.2, and 15.2.1.4.3](#), respectively.

An overview of demography and baseline characteristics is shown for the Safety Population and FAS in [Table 23](#), and the PP Set for each period in [Table 24, Table 25, Table 26, and Table 27](#).


Table 23 Summary of Demographic Data –FAS and Overall Safety Population

		FAS			Overall Safety (N=175)	Overall FAS (N=160)
Variable	Statistic	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)		
Sex						
Male	n (%)	45 (57.7)	25 (59.5)	22 (55.0)	102 (58.3)	92 (57.5)
Female	n (%)	33 (42.3)	17 (40.5)	18 (45.0)	73 (41.7)	68 (42.5)
Age (years)						
	Mean (SD)	37.1 (10.58)	37.4 (11.23)	37.0 (9.96)	37.7 (10.86)	37.2 (10.54)
	Median	37.0	37.0	38.0	38.0	37.5
	Min, Max	23, 65	23, 64	23, 55	23, 65	23, 65
Height (m)						
	Mean (SD)	1.655 (0.0748)	1.660 (0.1012)	1.650 (0.0781)	1.658 (0.0840)	1.655 (0.0829)
	Median	1.655	1.660	1.650	1.660	1.655
	Min, Max	1.52,1.84	1.47, 1.88	1.50, 1.80	1.47, 1.88	1.47, 1.88
Weight (kg)						
	Mean (SD)	62.87 (10.976)	61.99 (10.228)	61.36 (11.090)	62.39 (10.852)	62.26 (10.765)
	Median	61.55	63.80	59.95	61.30	61.40
	Min, Max	45.1, 97.8	43.4, 84.4	43.7, 91.8	43.4, 97.8	43.4, 97.8
BMI (kg/m ²)						
	Mean (SD)	22.85 (2.963)	22.44 (2.876)	22.48 (3.386)	22.62 (3.044)	22.65 (3.039)
	Median	22.40	21.90	21.30	21.90	21.90
	Min, Max	18.7, 32.7	18.9, 28.4	18.5, 31.8	18.5, 32.7	18.5, 32.7
Underweight	n (%)	0	0	0		0
Normal weight	n (%)	60 (76.9)	32 (76.2)	32 (80.0)	124 (77.5)	137 (78.3)
Overweight	n (%)	17 (21.8)	10 (23.8)	7 (17.5)	34 (21.3)	35 (20.0)
Obese	n (%)	1 (1.3)	0	1 (2.5)	2 (1.3)	2 (1.7)
Cigarette consumption						
10 to 19 cig/day	n (%)	40 (51.3)	23 (54.8)	21 (52.5)	93 (53.1)	84 (52.5)

**Table 23 Summary of Demographic Data –FAS and Overall Safety Population**

Variable	Statistic	FAS			Overall Safety (N=175)	Overall FAS (N=160)
		THS m2.2 (N=78)	mCC (N=42)	SA (N=40)		
>19 cig/day	n (%)	38 (48.7)	19 (45.2)	19 (45.7)	82 (46.9)	76 (47.5)
ISO tar yields	Mean (SD)	4.9 (3.53)	4.9 (3.79)	4.7 (3.79)	4.8 (3.66)	4.9 (3.65)
	Median	5.0	5.0	5.0	5.0	5.0
	Min, Max	1, 12	1, 12	1, 12	1, 12	1, 12
1 to 5 mg	n (%)	46 (59.0)	22 (52.4)	23 (57.5)	101 (57.7)	91 (56.9)
6 to 8 mg	n (%)	21 (26.9)	14 (13.3)	12 (30.0)	51 (29.1)	47 (29.4)
9 to 10 mg	n (%)	7 (9.0)	4 (9.5)	2 (5.0)	13 (7.4)	13 (8.1)
>10 mg	n (%)	4 (5.1)	2 (4.8)	3 (7.5)	10 (5.7)	9 (5.6)
ISO nicotine yields	Mean (SD)	0.40 (0.272)	0.40 (0.277)	0.39 (0.290)	0.32 (0.260)	0.40 (0.276)
	Median	0.40	0.45	0.40	0.10	0.40
	Min, Max	0.1, 1.0	0.1, 0.9	0.1, 0.9	0.1, 0.8	0.1, 1.0
≤0.6 mg	n (%)	63 (80.8)	30 (75.0)	30 (75.0)	14 (93.3)	125 (78.1)
>0.6 mg	n (%)	15 (19.2)	10 (25.0)	10 (25.0)	1 (6.7)	35 (21.9)

Abbreviations: BMI = body mass index; FAS = Full Analysis Set; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Tables 15.2.1.4.1 and 15.2.1.4.2](#)


Table 24 Summary of Demographic Data – PP Set: Period 1

Variable	Statistic	Overall PP Set (N=157)	Study Arm		
			THS m2.2 (N=76)	mCC (N=42)	SA (N=39)
Sex					
Male	n (%)	90 (57.3)	43 (56.6)	25 (59.5)	22 (56.4)
Female	n (%)	67 (42.7)	33 (43.4)	17 (40.5)	17 (43.6)
Age (years)	Mean (SD)	37.3 (10.57)	37.2 (10.69)	37.4 (11.23)	37.4 (9.83)
	Median	38.0	37.0	37.0	38.0
	Min, Max	23, 65	23, 65	23, 64	23, 55
Height (m)	Mean (SD)	1.655 (0.0829)	1.653 (0.0750)	1.660 (0.1012)	1.653 (0.0774)
	Median	1.650	1.650	1.660	1.650
	Min, Max	1.47, 1.88	1.52, 1.84	1.47, 1.88	1.50, 1.80
Weight (kg)	Mean (SD)	62.21 (10.668)	62.61 (10.835)	61.99 (10.228)	61.68 (11.044)
	Median	61.40	61.55	63.80	61.00
	Min, Max	43.4, 97.8	45.1, 97.8	43.4, 84.4	43.7, 91.8
BMI (kg/m ²)	Mean (SD)	22.64 (3.015)	22.80 (2.905)	22.44 (2.876)	22.53 (3.411)
	Median	21.90	22.40	21.90	21.30
	Min, Max	18.5, 32.7	18.7, 32.7	18.9, 28.4	18.5, 31.8
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	122 (77.7)	59 (77.6)	32 (76.2)	31 (79.5)
Overweight	n (%)	33 (21.0)	16 (21.1)	10 (23.8)	7 (17.9)
Obese	n (%)	2 (1.3)	1 (1.3)	0	1 (2.6)
Cigarette consumption					
10 to 19 cig/day	n (%)	82 (52.2)	39 (51.3)	23 (54.8)	20 (51.3)

**Table 24 Summary of Demographic Data – PP Set: Period 1**

Variable	Statistic	Overall PP Set (N=157)	Study Arm		
			THS m2.2 (N=76)	mCC (N=42)	SA (N=39)
>19 cig/day	n (%)	75 (47.8)	37 (48.7)	19 (45.2)	19 (48.7)
ISO tar yields	Mean (SD)	4.9 (3.66)	4.9 (3.52)	4.9 (3.79)	4.7 (3.88)
	Median	5.0	5.0	5.0	5.0
	Min, Max	1, 12	1, 12	1, 12	1, 12
1 to 5 mg	n (%)	89 (56.7)	45 (59.2)	22 (52.4)	22 (56.4)
6 to 8 mg	n (%)	47 (29.9)	21 (27.6)	14 (33.3)	12 (30.8)
9 to 10 mg	n (%)	12 (7.6)	6 (7.9)	4 (9.5)	2 (5.1)
>10 mg	n (%)	9 (5.7)	4 (5.3)	2 (4.8)	3 (7.7)
ISO nicotine yields	Mean (SD)	0.39 (0.274)	0.40 (0.265)	0.40 (0.277)	0.39 (0.294)
	Median	0.40	0.40	0.45	0.40
	Min, Max	0.1, 1.0	0.1, 1.0	0.1, 0.9	0.1, 0.9
≤0.6 mg	n (%)	123 (78.3)	62 (81.6)	32 (76.2)	29 (74.4)
>0.6 mg	n (%)	34 (21.7)	14 (18.4)	10 (23.8)	10 (25.6)

Abbreviations: BMI = body mass index; Max = maximum; mCC = menthol conventional cigarette; Min = minimum;

PP Set = per protocol set; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Tables 15.2.1.4.3](#)


Table 25 Summary of Demographic Data – PP Set: Period 2

Variable	Statistic	Overall PP Set (N=154)	Study Arm		
			THS m2.2 (N=74)	mCC (N=41)	SA (N=39)
Sex					
Male	n (%)	88 (57.1)	42 (56.8)	24 (58.5)	22 (56.4)
Female	n (%)	66 (42.9)	32 (43.2)	17 (41.5)	17 (43.6)
Age (years)	Mean (SD)	37.5 (10.56)	37.4 (10.75)	37.7 (11.14)	37.4 (9.83)
	Median	38.0	37.5	39.0	38.0
	Min, Max	23, 65	23, 65	23, 64	23, 55
Height (m)	Mean (SD)	1.654 (0.0830)	1.652 (0.0758)	1.658 (0.1007)	1.653 (0.0774)
	Median	1.650	1.650	1.660	1.650
	Min, Max	1.47, 1.88	1.52, 1.84	1.47, 1.88	1.50, 1.80
Weight (kg)	Mean (SD)	62.22 (10.771)	62.62 (10.981)	62.01 (10.354)	61.68 (11.044)
	Median	61.45	61.55	63.90	61.00
	Min, Max	43.4, 97.8	45.1, 97.8	43.4, 84.4	43.7, 91.8
BMI (kg/m ²)	Mean (SD)	22.67 (3.031)	22.83 (2.939)	22.51 (2.868)	22.53 (3.411)
	Median	21.90	22.40	21.90	21.30
	Min, Max	18.5, 32.7	18.7, 32.7	18.9, 28.4	18.5, 31.8
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	119 (77.3)	57 (77.0)	31 (75.6)	31 (79.5)
Overweight	n (%)	33 (21.4)	16 (21.6)	10 (24.4)	7 (17.9)
Obese	n (%)	2 (1.3)	1 (1.4)	0	1 (2.6)
Cigarette consumption					
10 to 19 cig/day	n (%)	81 (52.6)	38 (51.4)	23 (56.1)	20 (51.3)


Table 25 Summary of Demographic Data – PP Set: Period 2

Variable	Statistic	Overall PP Set (N=154)	Study Arm		
			THS m2.2 (N=74)	mCC (N=41)	SA (N=39)
>19 cig/day	n (%)	73 (47.4)	36 (48.6)	18 (43.9)	19 (48.7)
ISO tar yields	Mean (SD)	4.9 (3.67)	4.9 (3.52)	4.9 (3.83)	4.7 (3.88)
	Median	5.0	5.0	5.0	5.0
	Min, Max	1, 12	1, 12	1, 12	1, 12
1 to 5 mg	n (%)	88 (57.1)	44 (59.5)	22 (53.7)	22 (56.4)
6 to 8 mg	n (%)	45 (29.2)	20 (27.0)	13 (31.7)	12 (30.8)
9 to 10 mg	n (%)	12 (7.8)	6 (8.1)	3 (9.8)	2 (5.1)
>10 mg	n (%)	9 (5.8)	4 (5.4)	2 (4.9)	3 (7.7)
ISO nicotine yields	Mean (SD)	0.39 (0.274)	0.40 (0.264)	0.39 (0.280)	0.39 (0.294)
	Median	0.40	0.40	0.40	0.40
	Min, Max	0.1, 1.0	0.1, 1.0	0.1, 0.9	0.1, 0.9
≤0.6 mg	n (%)	121 (78.6)	61 (82.4)	31 (75.6)	29 (74.4)
>0.6 mg	n (%)	33 (21.4)	13 (17.6)	10 (24.4)	10 (25.6)

Abbreviations: BMI = body mass index; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Tables 15.2.1.4.3](#)

**Table 26 Summary of Demographic Data – PP Set: Period 3**

Variable	Statistic	Overall PP Set (N=150)	Study Arm		
			THS m2.2 (N=71)	mCC (N=41)	SA (N=38)
Sex					
Male	n (%)	86 (57.3)	41 (57.7)	24 (58.5)	21 (55.3)
Female	n (%)	64 (42.7)	30 (42.3)	17 (41.5)	17 (44.7)
Age (years)	Mean (SD)	37.7 (10.59)	37.7 (10.80)	37.7 (11.14)	37.6 (9.83)
	Median	39.0	39.0	39.0	38.5
	Min, Max	23, 65	23, 65	23, 64	23, 55
Height (m)	Mean (SD)	1.653 (0.0823)	1.650 (0.0732)	1.658 (0.1007)	1.653 (0.0784)
	Median	1.650	1.650	1.660	1.660
	Min, Max	1.47, 1.88	1.52, 1.84	1.47, 1.88	1.50, 1.80
Weight (kg)	Mean (SD)	62.28 (10.735)	62.67 (10.863)	62.01 (10.354)	61.83 (11.152)
	Median	61.90	62.10	63.90	61.20
	Min, Max	43.4, 97.8	45.1, 97.8	43.4, 84.4	43.7, 91.8
BMI (kg/m ²)	Mean (SD)	22.71 (3.048)	22.90 (2.956)	22.51 (2.868)	22.58 (3.445)
	Median	21.95	22.50	21.90	21.35
	Min, Max	18.5, 32.7	18.7, 32.7	18.9, 28.4	18.5, 31.8
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	115 (76.7)	54 (76.1)	31 (75.6)	30 (78.9)
Overweight	n (%)	33 (22.0)	16 (22.5)	10 (24.4)	7 (18.4)
Obese	n (%)	2 (1.3)	1 (1.4)	0	1 (2.6)
Cigarette consumption					
10 to 19 cig/day	n (%)	79 (52.7)	36 (50.7)	23 (56.1)	20 (52.6)

**Table 26 Summary of Demographic Data – PP Set: Period 3**

Variable	Statistic	Overall PP Set (N=150)	Study Arm		
			THS m2.2 (N=71)	mCC (N=41)	SA (N=38)
>19 cig/day	n (%)	71 (47.3)	35 (49.3)	18 (43.9)	18 (47.4)
ISO tar yields	Mean (SD)	4.9 (3.68)	5.1 (3.53)	4.9 (3.83)	4.6 (3.89)
	Median	5.0	5.0	5.0	4.5
	Min, Max	1, 12	1, 12	1, 12	1, 12
1 to 5 mg	n (%)	85 (56.7)	41 (57.7)	22 (53.7)	22 (57.9)
6 to 8 mg	n (%)	44 (29.3)	20 (28.2)	13 (31.7)	11 (28.9)
9 to 10 mg	n (%)	12 (8.0)	6 (8.5)	4 (9.8)	2 (5.3)
>10 mg	n (%)	9 (6.0)	4 (5.6)	2 (4.9)	3 (7.9)
ISO nicotine yields	Mean (SD)	0.40 (0.275)	0.41 (0.266)	0.39 (0.280)	0.38 (0.294)
	Median	0.40	0.40	0.40	0.35
	Min, Max	0.1, 1.0	0.1, 1.0	0.1, 0.9	0.1, 0.9
≤0.6 mg	n (%)	117 (78.0)	57 (80.3)	31 (75.6)	29 (76.3)
>0.6 mg	n (%)	33 (22.0)	14 (19.7)	10 (24.4)	9 (23.7)

Abbreviations: BMI = body mass index; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Tables 15.2.1.4.3](#)


Table 27 Summary of Demographic Data – PP Set: Period 4

Variable	Statistic	Overall PP Set (N=148)	Study Arm		
			THS m2.2 (N=70)	mCC (N=41)	SA (N=37)
Sex					
Male	n (%)	84 (56.8)	39 (55.7)	24 (58.5)	21 (56.8)
Female	n (%)	64 (43.2)	31 (44.3)	17 (41.5)	16 (43.2)
Age (years)	Mean (SD)	37.8 (10.55)	37.7 (10.68)	37.7 (11.14)	37.8 (9.91)
	Median	39.0	38.5	39.0	39.0
	Min, Max	23, 65	23, 65	23, 64	23, 55
Height (m)	Mean (SD)	1.654 (0.0842)	1.651 (0.0773)	1.658 (0.1007)	1.655 (0.0788)
	Median	1.650	1.650	1.660	1.670
	Min, Max	1.47, 1.88	1.52, 1.84	1.47, 1.88	1.50, 1.80
Weight (kg)	Mean (SD)	62.23 (10.803)	62.35 (11.097)	62.01 (10.354)	62.24 (11.013)
	Median	61.60	61.55	63.90	61.40
	Min, Max	43.4, 97.8	45.1, 97.8	43.4, 84.4	43.7, 91.8
BMI (kg/m ²)	Mean (SD)	22.67 (3.038)	22.76 (2.958)	22.51 (2.868)	22.69 (3.424)
	Median	21.90	22.20	21.90	21.40
	Min, Max	18.7, 32.7	18.7, 32.7	18.9, 28.4	18.7, 31.8
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	115 (77.7)	55 (78.6)	31 (75.6)	29 (78.4)
Overweight	n (%)	31 (20.9)	14 (20.0)	10 (24.4)	7 (18.9)
Obese	n (%)	2 (1.4)	1 (1.4)	0	1 (2.7)
Cigarette consumption					
10 to 19 cig/day	n (%)	79 (53.4)	36 (51.4)	23 (56.1)	20 (54.1)

**Table 27 Summary of Demographic Data – PP Set: Period 4**

Variable	Statistic	Overall PP Set (N=148)	Study Arm		
			THS m2.2 (N=70)	mCC (N=41)	SA (N=37)
>19 cig/day	n (%)	69 (46.6)	34 (48.6)	18 (43.9)	17 (45.9)
ISO tar yields	Mean (SD)	4.8 (3.69)	4.9 (3.53)	4.9 (3.83)	4.5 (3.90)
	Median	5.0	5.0	5.0	4.0
	Min, Max	1, 12	1, 12	1, 12	1, 12
1 to 5 mg	n (%)	86 (58.1)	42 (60.0)	22 (53.7)	22 (59.5)
6 to 8 mg	n (%)	42 (28.4)	19 (27.1)	13 (31.7)	10 (27.0)
9 to 10 mg	n (%)	11 (7.4)	5 (7.1)	4 (9.8)	2 (5.4)
>10 mg	n (%)	9 (6.1)	4 (5.7)	2 (4.9)	3 (8.1)
ISO nicotine yields	Mean (SD)	0.39 (0.270)	0.39 (0.256)	0.39 (0.280)	0.37 (0.293)
	Median	0.40	0.40	0.40	0.30
	Min, Max	0.1, 1.0	0.1, 1.0	0.1, 0.9	0.1, 0.9
≤0.6 mg	n (%)	119 (80.4)	59 (84.3)	31 (75.6)	29 (78.4)
>0.6 mg	n (%)	29 (19.6)	11 (15.7)	10 (24.4)	8 (21.6)

Abbreviations: BMI = body mass index; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; N = number of subjects; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Tables 15.2.1.4.3](#)



All subjects were Japanese with comparable mean age, height, weight, and BMI between the THS 2.2 Menthol, mCC, and SA arms in the FAS at baseline.

The BMI data are further summarized 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 ($\geq 30.0 \text{ kg/m}^2$).

The data for the PP Set are further summarized by sex and cigarette consumption in [Appendix 15](#), [Table 15.2.1.4.3.1](#) and [Table 15.2.1.4.3.2](#), respectively.

The mean age across the study arms at baseline ranged from 35.4 to 38.0 years for males and from 36.6 to 40.2 years for females (PP Set Period 1). The mean BMI across the study arms at baseline ranged from 22.75 to 23.49 kg/m^2 for males and from 21.92 to 21.98 kg/m^2 .

The mean age across the study arms at baseline ranged from 35.6 to 38.6 years for subjects who smoked 10 to 19 cigarettes/day and 35.9 to 38.8 years for subjects who smoked >19 cigarettes/day. The mean BMI across the study arms at baseline ranged from 22.34 to 22.57 kg/m^2 for subjects who smoked 10 to 19 cigarettes/day and from 22.27 to 23.11 kg/m^2 for subjects who smoked >19 cigarettes/day.

The number of male and female subjects and the number of subjects in each BMI category, mCC consumption category, and ISO tar and nicotine yields categories were comparable for each study arm at baseline. In addition, the mean age, height, weight, BMI including categories, and mCC consumption of the PP Sets remained comparable for each period during the study ([Appendix 15](#), [Table 15.2.1.4.3](#)).

10.4.1.1 Socio-economic Status Questionnaire Data

Answers to the SES questions 1 to 5b are listed in [Appendix 15](#), [Listing 15.3.1.11](#) and are tabulated along with baseline characteristics data for the Safety Population, FAS, and PP Set in [Appendix 15](#), [Table 15.2.1.4.1](#), [Table 15.2.1.4.2](#), and [Table 15.2.1.4.3](#), respectively. A summary of the data for PP Set Period 1 is provided below.

Overall, the higher proportion of subjects (37.6%) lived in a household of 1, with 35 (46.1%), 12 (28.6%), and 12 (30.8%) subjects in THS 2.2 Menthol, mCC, and SA study arms, respectively. The next highest proportion of subjects (21.0%) lived in a household of 2, with 13 (17.1%), 7 (16.7%), and 13 (33.3%) subjects in THS 2.2 Menthol, mCC, and SA study arms, respectively.

The highest proportion of subjects in the study (40.1%) had or were currently attaining a University/Postgraduate level of education, with 30 (39.5%), 18 (42.9%), and 15 (38.5%) subjects in THS 2.2 Menthol, mCC, and SA study arms, respectively. Following this



category, subjects either had or were currently attaining a college (22.9%) or senior high school level of education (27.4%).

In the THS 2.2 Menthol arm, the majority of subjects had just 1 income earner in their household (46 [59.2%] subjects), and similar numbers of subjects in the mCC and SA arms had either 1 income or 2 or more incomes (20 [47.6%] subjects in the mCC arm for both categories, and 18 [46.2%] and 17 [43.6%] subjects in the SA arms for each category, respectively).

In the study, there were a number of different occupations, with the higher proportion of subjects in each arm being part-time workers (more than 1 day per week), with 20 (26.3%), 7 (16.7%), and 10 (25.6%) subjects in the THS 2.2 Menthol, mCC, and SA arms, respectively.

Of those subjects who reported their approximate monthly household income from all sources before tax the highest proportion (16.6%) reported an amount of 200,000 Yen to 299,999 Yen, with 15 (19.7%), 4 (9.5%), and 7 (17.9%) subjects in THS 2.2 Menthol, mCC, and SA study arms, respectively.

10.4.2 Medical and Surgical History

Medical history is tabulated by subject in [Appendix 15, Listing 15.3.1.9](#) and summarized by SOC and PT for the Safety Population in [Appendix 15, Table 15.2.1.6](#).

Clinically relevant medical history was to be reported at the Screening Visit, with 13 subjects (7.4%) reporting medical history findings; 6 subjects (7.7%) in the THS 2.2 Menthol arm, no subjects in the mCC arm, 5 subjects (12.5%) in the SA arm, and 2 subjects who were enrolled and tested the study product, but were not randomized.

The most frequent medical history findings by SOC were injury, poisoning, and procedural complications (2 subjects [2.6%] in the THS 2.2 Menthol arm, no subjects in the mCC arm, and 3 subjects [7.5%] in the SA arm), then Infections and Infestations, surgical and medical procedures, and reproductive system and breast disorder.

The most frequent medical history findings by PT were clavicle fracture, appendicitis, tonsillectomy, ovarian cyst, which were all reported by 2 subjects each. All other medical histories were reported by a maximum of 1 subject each.

Of those enrolled and randomized, there were no medical history findings of clinical concern.



10.4.3 CYP2A6 Activity at Baseline

Cytochrome P450 2A6 activity in plasma at baseline, Period 1 (Day 0) is listed by subject in [Appendix 15, Listing 15.3.6.16](#) and summarized for the PP Set and FAS in [Appendix 15, Table 15.2.4.44.1](#) and [Table 15.2.4.44.2](#), respectively.

No relevant differences were observed between the 3 study arms, with regard to baseline CYP2A6 activity in either the PP Sets (Periods 1 and 4) or the FAS.

Randomized subjects in the PP Set (Period 1) with evaluable CYP2A6 data had a mean baseline CYP2A6 activity of 26.23% (SD = 16.294%, minimum = 4.1%, maximum = 96.2%) for the THS 2.2 Menthol arm, 28.53% (SD = 14.414%, minimum = 5.1%, maximum = 70.9%) for the mCC arm, and 26.05% (SD = 14.581%, minimum = 6.4%, maximum = 58.5%) for the SA arm.

10.4.4 Fagerström Test for Nicotine Dependence at Screening

Individual subject responses to the FTND are listed by study arm in [Appendix 15, Listing 15.3.6.11](#).

The FTND overall classification is summarized by category (mild: 0 to 3; moderate: 4 to 6; severe: 7 to 10) at baseline for the Safety Population and FAS in [Appendix 15, Table 15.2.1.4.1](#), and [Appendix 15, Table 15.2.1.4.2](#), respectively. In addition, the FTND overall classification is summarized as above for the PP Set for each period (1 to 4) in [Appendix 15, Table 15.2.1.4.3](#). Data for the PP Set in Period 1 are also provided in [Table 28](#).

Table 28 Fagerström Test of Nicotine Dependence (PP Set Period 1)

FTND Score	Statistic	Study Arm		
		THS m2.2 (N=76)	mCC (N=42)	SA (N=39)
	N	76	42	38
	Mean	4.3	4.3	4.7
	SD	1.81	1.81	2.11
	Median	4.0	4.0	5.0
	Min, Max	1, 9	1, 8	0, 9
Mild (n [%])		27 (35.5)	17 (40.5)	8 (20.5)
Moderate (n [%])		42 (55.3)	18 (42.9)	22 (56.4)
Severe (n [%])		7 (9.2)	7 (16.7)	8 (20.5)

Abbreviations: FTND = Fagerström Test of Nicotine Dependence; max = maximum; min = minimum; mCC = Menthol conventional cigarette; N = number of subjects; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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



At baseline, the majority of subjects were classified as moderate (55.3%) in the THS 2.2 Menthol arm (N=76), with 35.5% and 9.2% classified as mild and severe, respectively; in the mCC arm (N=42), 42.9% were classified as moderate, with 40.5% and 16.7% classified as mild and severe, respectively; and in the SA arm (N=39) 56.4% were classified as moderate, with 20.5% classified as mild and severe. Of those that were classified as severe, 9 were male and 13 were female, and 4 smoked 10 to 19 cigarettes/day and 18 smoked >19 cigarettes/day.

The results of the overall Safety Population and the FAS were consistent with the PP Set at baseline (Periods 1 to 4), with the majority of the subjects classified as having a moderate dependence on nicotine (53.1%).

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 -2), are listed by study arm in [Appendix 15, Listing 15.3.1.2](#).

The ISO tar yields (mg) recorded at Admission (Day -2) 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 Population and FAS in [Appendix 15, Table 15.2.1.4.1](#), and [Appendix 15, Table 15.2.1.4.2](#), respectively. In addition, the ISO tar yields (mg) are summarized as above for the PP Set for each period baseline (1 to 4) in [Appendix 15, Table 15.2.1.4.3](#).

The current mCC brand names recorded at Screening and Admission (Day -2) are summarized for the Screening data in [Appendix 15, Table 15.2.1.5](#).

In the Safety Population and FAS, the majority of enrolled subjects smoked CC with an ISO tar yield of 1 to 5 mg (101 subjects, 57.7% for the Safety Population, and 91 subjects, 56.9% for the FAS). In general, the distribution of subjects in each ISO tar yield category was comparable between the THS 2.2 Menthol, mCC, and SA arms.

In the PP Set (Period 1), the majority of subjects smoked CC with an ISO tar yield of 1 to 5 mg (89 subjects, 56.7%); and the distribution of subjects in each ISO tar yield category was comparable between the THS 2.2 Menthol, mCC, and SA arms. The distribution of male and female subjects within the PP Set who smoked CC with an ISO tar yield of 6 to 8 mg was generally similar. However, the number of male subjects (38 subjects, 42.2%) who smoked CC with an ISO tar yield of 1 to 5 mg was lower than the number of female subjects (51 subjects, 76.1%). No female subjects smoked cigarettes with an ISO tar yield of 9 to 10 mg, whereas, 12 male subjects (13.3%) smoked CC with an ISO tar yield of 9 to 10 mg, 8 males (8.9%) smoked cigarettes with an ISO tar yield of >10 mg, and 1 female (1.5%) smoked CC with an ISO tar yield of >10 mg. Consistent results were observed at baseline for each PP Set period.



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 -2), are listed by study arm 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 was categorized into 10 to 19 or >19 cigarettes/day at baseline. The number of subjects who smoked 10 to 19 and >19 cigarettes/day at baseline are summarized in [Table 22 in Section 10.3](#).

10.4.7 Other Baseline Data

The following baseline data are listed by study arm for all subjects ([Appendix 15, Listing 15.3.1.6](#)):

- Chest X-ray findings at the Screening Visit were normal for all enrolled subjects.
- Urine cotinine screen at the Screening Visit and at Admission (Day -2) were positive for all enrolled subjects.
- Urine drug screen and alcohol breath test at the Screening Visit and at Admission (Day -2) were negative for all enrolled subjects.
- Serology tests at the Screening Visit: tests for HBsAg, and HCV were negative for all enrolled subjects, with the exception of 1 subject who tested positive for HCV at Screening and was discontinued (SEI-0086). Results of the HIV 1/2 serology tests could not be transferred to the CRO due to Japanese privacy laws; therefore, these results are not tabulated in listings.
- Urine pregnancy test results at the Screening Visit, Admission (Day -2), and on the Day of Discharge were negative for all 73 female subjects in the overall Safety Population or the female was confirmed postmenopausal.

10.4.8 Concomitant Diseases

Concomitant diseases are tabulated by subject in [Appendix 15, Listing 15.3.1.9](#) and summarized for the Safety Population in [Appendix 15, Table 15.2.1.7](#) and [Table 29](#).

**Table 29 Concomitant Diseases by System Organ Class (Safety Population)**

System Organ Class	Study Arm			Product Test Only (N=15)	Overall Safety (N=175)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)		
Number (%) subjects with any concomitant disease	13 (16.7%)	4 (9.5%)	4 (10.0%)	2 (13.3%)	23 (13.1%)
Vascular disorders	3 (3.8%)	1 (2.4%)	1 (2.5%)	0	5 (2.9%)
Gastrointestinal disorders	1 (1.3%)	1 (2.4%)	2 (5.0%)	0	4 (2.3%)
Metabolism and nutrition disorders	3 (3.8%)	0	0	0	3 (1.7%)
Skin and subcutaneous tissue disorders	2 (2.6%)	0	1 (2.5%)	0	3 (1.7%)
Cardiac disorders	0	0	1 (2.5%)	1 (6.7%)	2 (1.1%)
Immune system disorders	1 (1.3%)	1 (2.4%)	0	0	2 (1.1%)
Nervous system disorders	1 (1.3%)	1 (2.4%)	0	0	2 (1.1%)
Blood and lymphatic system disorders	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	0	0	0	1 (6.7%)	1 (0.6%)
Neoplasms benign, malignant, unspecified (including cysts and polyps)	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: mCC = Menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.1.7](#).

For the overall Safety Population (N=175), 23 subjects reported concomitant diseases at Screening (defined as any condition that started prior to the Screening Visit and was still ongoing at the Screening Visit).

The incidence of concomitant diseases was lower in the mCC and SA arms than in the THS 2.2 Menthol arm; however, the difference in prevalence of concomitant diseases was not of concern for the analysis of study results.

The most frequent was hypotension reported by 5 subjects (3 subjects [3.8%] in the THS 2.2 Menthol arm, 1 subject [2.4%] in the mCC arm and 1 subject [2.5%] in the SA arm) and constipation reported by 4 subjects (1 subject each in the THS 2.2 Menthol and mCC arms [1.3% and 2.4%, respectively], and 2 subjects [5.0%] in the SA arm). All other reported concomitant diseases were reported by 2 or fewer subjects.



10.4.9 Prior and Concomitant Medications

Prior and concomitant medications (pre-randomization, and post-randomization) are listed for all subjects in [Appendix 15, Listing 15.3.6.3](#). No prior medications were reported in this study.

Concomitant medications (pre-randomization and post-randomization) are summarized by ATC in [Appendix 15, Table 15.2.6.19.1](#) and by preferred drug name in [Appendix 15, Table 15.2.6.19.2](#).

The only concomitant medications started pre-randomization were by 1 subject who was enrolled and tested the drug product but was not randomized ([Table 30](#)).

Table 30 Concomitant Medications (Safety Population) – Pre-Randomization

ATC1 ATC2	Study Arm			Product Test only (N=15)	Overall Safety (N=175)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)		
Number (%) subjects with any prior medication	0	0	0	1 (6.7%)	1 (0.6%)
Alimentary Track and Metabolism	0	0	0	1 (6.7%)	1 (0.6%)
Stomatological Preparations				1 (6.7%)	1 (0.6%)
Nervous system	0	0	0	1 (6.7%)	1 (0.6%)
Analgesics				1 (6.7%)	1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.19.1](#).

Concomitant medications started during the Confinement Period are summarized in [Table 31](#) and those started during the Ambulatory Period are summarized in [Table 32](#).

**Table 31 Concomitant Medications (Safety Population) – Confinement Period**

ATC1 ATC2	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)	
Number (%) subjects with any post-randomization concomitant medication	2 (2.6%)	0	3 (7.5%)	5 (3.1%)
Antiinfectives for systemic use	0	0	2 (5.0%)	2 (1.3%)
Antibacterials for systemic use			2 (5.0%)	2 (1.3%)
Nervous system	0	0	2 (5.0%)	2 (1.3%)
Analgesics			2 (5.0%)	2 (1.3%)
Alimentary tract and metabolism	1 (1.3%)	0	0	1 (0.6%)
Drugs for constipation	1 (1.3%)			1 (0.6%)
Sensory Organs	1 (1.3%)	0	0	1 (0.6%)
Ophthalmologicals	1 (1.3%)			1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; mCC = Menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.19.1](#)

The most common concomitant medications during the Confinement Period were antibacterials for systemic use and analgesics, which were both started by 2 subjects each, both in the SA arm.

All other concomitant medications were started by a maximum of 1 subject in each study arm.

None of the medications started in the Confinement Period were assessed to have had an impact on 11-DTX-B2, CYP1A2, or CYP2A6.

**Table 32 Concomitant Medications (Safety Population) – Ambulatory Period**

ATC1 ATC2	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)	
Number (%) subjects with any post-randomization concomitant medication	9 (11.5%)	5 (11.9%)	3 (7.5%)	17 (10.6%)
Nervous system	3 (3.8%)	3 (7.1%)	1 (2.5%)	7 (4.4%)
Analgesics	3 (3.8%)	3 (7.1%)	1 (2.5%)	7 (4.4%)
Alimentary tract and metabolism	2 (2.6%)	2 (4.8%)	2 (5.0%)	6 (3.8%)
Drugs for acid related disorders	0	1 (2.4%)	1 (2.5%)	2 (1.3%)
Stomatological preparations	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Antidiarrheals, intestinal anti-inflammatory/ antiinfective agents	0	0	1 (2.5%)	1 (0.6%)
Other alimentary tract and metabolism products	1 (1.3%)	0	0	1 (0.6%)
Antiinfectives for systemic use	3 (3.8%)	1 (2.4%)	2 (5.0%)	6 (3.8%)
Antibacterials for systemic use	3 (3.8%)	1 (2.4%)	2 (5.0%)	6 (3.8%)
Respiratory system	5 (6.4%)	0	1 (2.5%)	6 (3.8%)
Cough and cold preparations	2 (2.6%)		1 (2.5%)	3 (1.9%)
Throat preparations	3 (3.8%)		0	3 (1.9%)
Antihistamines for systemic use	1 (1.3%)		0	1 (0.6%)
Nasal preparations	1 (1.3%)		0	1 (0.6%)
Blood and blood forming organs	0	2 (4.8%)	2 (5.0%)	4 (2.5%)
Antianemic preparations		2 (4.8%)	0	2 (1.3%)
Antihemorrhagics		0	2 (5.0%)	2 (1.3%)
Musculo-skeletal system	2 (2.6%)	1 (2.4%)	1 (2.5%)	4 (2.5%)
Anti-inflammatory and antirheumatic products	1 (1.3%)	1 (2.4%)	1 (2.5%)	3 (1.9%)
Topical products for joint and muscular pain	1 (1.3%)	0	0	1 (0.6%)
Cardiovascular system	0	1 (2.4%)	0	1 (0.6%)
Lipid modifying agents		1 (2.4%)		
Dermatologicals	1 (1.3%)	0	0	1 (0.6%)
Anti-acne preparations	1 (1.3%)			1 (0.6%)
Corticosteroids, dermatological preparations	1 (1.3%)			1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; mCC = Menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.19.1](#)



The most common concomitant medications started during the Ambulatory Period were analgesics, which were taken by 7 subjects (3 subjects [3.8%] in the THS 2.2 Menthol arm, 3 subjects [7.1%] in the mCC arm, and 1 subject [2.5%] in the SA arm), followed by antibacterials for systemic use medications taken by 6 subjects (3 subjects [3.8%] in the THS 2.2 Menthol arm, 1 subject [2.4%] in the mCC arm, and 2 subjects [5.0%] in the SA arm), throat preparations taken by 3 subjects (3 subjects [3.8%] in the THS 2.2 Menthol arm), cough and cold preparations taken by 3 subjects (2 subjects [2.6%] in the THS 2.2 Menthol arm and 1 subject [2.5%] in the SA arm), anti-inflammatory and antirheumatic products taken by 3 subjects (1 subject in each study arm [1.3%, 2.4%, and 2.5%, respectively]).

All other concomitant medications were started by a maximum of 2 subjects in each study arm.

There were a number of medications administered during the Ambulatory Period known to have an impact on 11-DTX-B2, CYP1A2, or CYP2A6. Those that were taken within 5 half-lives of an assessment were stomatological and mouth preparations, which affects CYP1A2 and CYP2A6 (within 2 hours of an assessment), pabron S gold which affects CYP1A2 and CYP2A6 (within 5 hours of an assessment), diclofenac which affects 11-DTX-B2 and CYP1A2 (within 2 hours of an assessment), and loxoprofen sodium which affects 11-DTX-B2 (within 1.1 hours of an assessment). Other medications known to affect 11-DTX-B2, CYP1A2, and CYP2A6 but were outside of 5 half-lives exclusion period were clarithromycin, dextromethorphan hydrobromide, garenoxacin mesilate, and nadifloxacin ([Appendix 15, Listing 15.3.6.3](#)). Analysis on CYP1A2, CYP2A6, and 11-DTX-B2 has been performed with and without the data reported to be within 5 half-lives of an assessment ([Section 11](#)).

10.5 Extent of Exposure to Investigational Product

Details of the subjects' daily consumption of mCC, during the Confinement Period are tabulated in [Appendix 15, Listing 15.3.2.1.1](#). Details of the subjects' THS Menthol Tobacco Stick daily consumption during the Confinement Period, including the product trial at Admission (Day -2), are tabulated in [Appendix 15, Listing 15.3.2.1.2](#). Details of product usage during the Ambulatory Period are tabulated in [Appendix 15, Listing 15.3.2.1.3](#).

Descriptive statistics of daily product use in the Confinement Period are summarized in [Appendix 15, Table 15.2.2.1.1](#) for the FAS and [Table 15.2.2.1.2](#) for the PP Set. Descriptive statistics of maximum daily product use in the Ambulatory Period are summarized in [Appendix 15, Table 15.2.2.2](#) for the FAS. The average daily product use in the Ambulatory Period is summarized in [Appendix 15, Table 15.2.2.3.1](#) for the Safety Population, and [Table 15.2.2.3.2](#) for the PP Set. A summary of product use by product use compliance category in the Ambulatory Period is tabulated in [Appendix 15, Table 15.2.2.4](#) for the FAS and a summary of average daily product use by product use



compliance category is tabulated in [Appendix 15, Table 15.2.2.5.1](#) and [Table 15.2.2.5.2](#) for the FAS and the PP Set, respectively. Descriptive statistics of average daily product use in the Ambulatory Period by preferred product declared at Admission are summarized in [Appendix 15, Table 15.2.4.49](#) for the FAS and descriptive statistics of product use compliance categories by preferred product declared at Admission are summarized in [Appendix 15, Table 15.2.4.50](#) for the FAS.

Details of product compliance during the study are reported in [Section 10.6](#).

All enrolled subjects completed the product test at Admission (Day -2) using only 1 THS Menthol Tobacco Stick, with the exception of 1 subject (THS 2.2 Menthol arm) who used 2 sticks ([Appendix 15, Table 15.2.2.1.1](#)).

All subjects received the IP according to the randomization schedule. The number of THS Menthol Tobacco Sticks and mCC consumed during the Confinement Period are summarized for the PP Set in [Table 33](#).

Table 33 Average Number of THS Menthol Tobacco Sticks and Menthol Conventional Cigarettes Consumed Daily in the Confinement Period – PP Set Period 1

Study Arm	Visit	Number of Subjects	Arithmetic Mean (SD)	Min	Median	Max
THS m2.2	Day 0					
	(baseline, mCC use)	76	13.1 (3.83)	4	13.0	22
	Day 1	76	11.4 (3.91)	4	11.0	24
	Day 2	76	12.0 (4.14)	3	11.0	28
	Day 3	76	12.1 (3.76)	5	11.0	21
	Day 4	76	12.4 (3.84)	5	11.5	21
	Day 5	76	13.9 (4.33)	6	13.0	22
mCC	Day 0 (baseline)	42	12.5 (3.87)	5	12.0	24
	Day 1	42	11.0 (4.01)	5	10.0	25
	Day 2	41	12.5 (4.16)	7	11.0	25
	Day 3	41	12.1 (4.17)	7	11.0	23
	Day 4	41	11.3 (3.96)	6	10.0	25
	Day 5	41	13.6 (4.68)	6	12.0	24

Abbreviations: Max = maximum; mCC = menthol conventional cigarette; Min = minimum; SD = standard deviation; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Tables 15.2.2.1.2](#)

At baseline the mean daily mCC consumed was 13.1 cigarettes/day in the THS 2.2 Menthol arm and 12.5 cigarettes/day in the mCC arm.



In the THS 2.2 Menthol arm, the mean number of THS Menthol Tobacco Sticks consumed daily increased from Day 1 (11.4 sticks/day) to Day 5 (13.9 sticks/day) in the Confinement Period. Similarly, in the mCC arm the mean number of mCC consumed daily increased from Day 1 (11.0 cigarettes/day) to Day 5 (13.6 cigarettes/day), with the mean daily consumption of THS Menthol Tobacco Sticks or mCC on Day 5 being similar between the 2 study arms.

The average reported daily number of THS Menthol Tobacco Sticks and mCC consumed during the Ambulatory Period are summarized for each period in [Table 34](#).

Table 34 Average Number of THS Menthol Tobacco Sticks and Menthol Conventional Cigarettes Consumed Daily in the Ambulatory Period

Study Arm	Visit	Number of Subjects	Mean (SD) ²	Min	Median	Max
Safety Population¹ (N=160)						
THS m2.2	Period 2	76	11.6 (6.11)	0	11.0	26
	Period 3	76	12.2 (6.42)	0	11.8	27
	Period 4	76	12.3 (6.65)	0	11.8	29
mCC	Period 2	41	13.8 (4.16)	8	12.9	24
	Period 3	41	14.9 (5.70)	7	14.2	39
	Period 4	41	15.2 (5.04)	9	14.1	35
PP Set						
THS m2.2	Period 2	74	11.7 (5.95)	0	11.0	26
	Period 3	71	12.7 (6.25)	0	11.9	27
	Period 4	70	12.7 (6.48)	0	12.0	29
mCC	Period 2	41	13.8 (4.16)	8	12.9	24
	Period 3	41	14.9 (5.70)	7	14.2	39
	Period 4	41	15.2 (5.04)	9	14.1	35

Abbreviations: CC = conventional cigarettes; FAS = Full Analysis Set; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; PP = per protocol; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Ambulatory Periods defined as Period 2 ([Day 6 Ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

[1] Safety Population post-randomization presented, which is the same as the FAS.

[2] Mean number of THS m2.2 consumed daily in the THS m2.2 study arm and mean number of CC/mCC consumed daily in the mCC arm presented.

Data Source: [Appendix 15, Tables 15.2.2.3.1 and 15.2.2.3.2](#)

In the Ambulatory Period, the FAS and Safety Populations were identical for both the THS 2.2 Menthol arm and the mCC arm.

During the Ambulatory Period, in the THS 2.2 Menthol arm, the mean number of sticks consumed daily during Periods 2, 3, and 4 was higher than Day 1 daily stick use



(11.4 sticks/day), with a mean 12.3 sticks/day reported during Period 4. In the mCC arm, the mean number of mCC consumed daily during Periods 2, 3, and 4 was greater than baseline (12.5 cigarettes/day) and Day 1 (11.0 cigarettes/day), with a mean 15.2 cigarettes/day reported during Period 4. For each period in the Ambulatory Setting, the mean reported daily number of THS Menthol Tobacco Sticks was lower than the mean reported daily number of mCCs consumed in the respective arms (Table 34).

10.6 Compliance to Investigational Product

Compliance to the assigned products in each study arm, and overall is tabulated for the FAS in Table 15.2.5.2. Summary of compliance, as measured by exhaled CO, for subjects in the SA arm during the Confinement Period is tabulated for the FAS in Appendix 15, Table 15.2.5.1. In addition, a summary of product use by product use compliance in each study arm and each period of the Ambulatory Period is tabulated in Appendix 15, Table 15.2.2.4.

10.6.1 Compliance to Investigational Product During the Confinement Period

Compliance during the Confinement Period was ensured by strict distribution of the products (product by product) and collection of THS Menthol Tobacco Sticks and CC butts.

In the THS 2.2 Menthol study arm (N=78) the 2 subjects who were not included in the Compliant Population (Table 35; Appendix 15, Table 15.2.5.2) were: 1 subject who withdrew on Day 1 (Section 10.3) and the mis-randomized subject who was not considered to have completed the Confinement Period as per protocol. The protocol deviation for misuse of product in Period 1 in the THS 2.2 Menthol study arm (Table 20) was related to the subject who withdrew, and therefore, all 77 subjects who did complete the Confinement Period had exclusive use of the assigned product as per Appendix 15, Listing 15.3.2.1.2.

In the mCC arm, 42 of 42 subjects had exclusive use of mCC during the Confinement Period (Table 35).

In the SA study arm (N=40), 1 subject did not complete the Confinement Period. Therefore, of the 39 subjects who did complete the Confinement Period, all 39 subjects were abstinent during the Confinement Period (Table 35). However, within the data (Appendix 15, Table 15.2.5.2), the subject who was not considered to have been abstinent was the subject who had withdrawn during this period (Section 10.3).

In the SA arm, compliance was also chemically verified using an exhaled CO breath test (subjects within the SA arm could use NRT). The exhaled CO levels (ppm) for subjects in the SA arm from Day -2 to Day of Discharge from the Confinement Period are listed in Appendix 15, Listing 15.3.3.2, with levels >10 ppm considered as non-compliant. A



summary of compliance as measured by exhaled CO levels in the SA arm during the Confinement Period are tabulated in [Appendix 15, Table 15.2.5.1](#).

In the SA arm, all subjects had exhaled levels of CO ≤ 10 ppm throughout the Confinement Period, Day 1 until Day 5.

10.6.2 Compliance to Investigational Product During the Ambulatory Period

Exclusive use of the assigned product during the Ambulatory Period is summarized in [Table 35](#).

In the THS 2.2 Menthol study arm during Periods 2, 3, and 4 (N=78) at least 82% of subjects exclusively used the assigned THS 2.2 Menthol product (Exclusive THS 2.2 product use category; [Table 35](#)), including the subject who was mis-randomized but was fully compliant throughout the Ambulatory Period (Subject TOK-0092; [Appendix 15, Listing 15.3.2.1.3](#)).

In the mCC study arm (N=42), 1 subject withdrew in Period 1, and all 41 subjects in Periods 2, 3, and 4 exclusively used the assigned product during the Ambulatory Period.

In the SA study arm (N=40), 1 subject withdrew in Period 1 and 1 subject withdrew in Period 3, therefore, all 39 subjects in Period 2 remained abstinent, and all 38 subjects in Periods 3 and 4 remained abstinent.

10.6.2.1 Product Use Category Classification During the Ambulatory Period

In addition to the above compliance assessment, classification of subject's product use during the Ambulatory Period was also assessed ([Table 36](#)).

Of the 78 subjects in the THS 2.2 Menthol study arm, at least 87.2% within each period and overall in the Ambulatory Safety Population were classified as THS 2.2 Menthol users, using the THS 2.2 Menthol product at least 70% of the time; at least 85.9% subjects were classified as primarily THS 2.2 Menthol users, using the THS 2.2 Menthol product $>95\%$ of the time. There were 2 subjects in Period 3 and 4 that were considered to be dual-balanced users ([40-60]%), and 2 subjects in Periods 2 and 3, and 3 subjects in Period 4 who were classified as CC users and used the THS 2.2 Menthol product $<30\%$ of the time (including Subject TOK-0035 [[Section 10.6.2](#)]). Lastly, there were 4 subjects in each of Periods 2 to 4, with a total of 5 subjects in the FAS, who were considered "Not abstinent"; these subjects reported use of e-cigarette products only.

Of the 42 subjects in the mCC arm, all 41 subjects who completed the study used CC exclusively in each period. Of note was Subject TOK-0035 of the THS 2.2 Menthol arm who was considered to have exclusive use of mCC during the Ambulatory Period,



because the subject did not complete the product use diary ([Appendix 15, Listing 15.3.2.1.2](#)).

Of the SA arm, at least 92.5% of subjects in each period and overall were abstinent, with 1 subject in Period 2 assessed as predominantly abstinent (not more than 0.5 uses of any tobacco or nicotine containing product per day on average, or not more than 2 uses on a single day), and 1 subject each in Period 3 and 4 assessed as not abstinent (more than 0.5 uses of any tobacco or nicotine containing product per day on average or more than 2 uses on a single day).


Table 35 Compliance to Assigned Product by Period and Overall - FAS

Compliance	Confinement		Ambulatory		Overall FAS n (%)
	Period 1 n (%)	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)	
THS m2.2 Arm - N	78	78	78	78	78
Exclusive product use ¹ - Yes	76 (97.4)	63 (80.8)	65 (83.3)	65 (83.3)	57 (73.1)
No	2 (2.6)	14 (17.9)	12 (15.4)	12 (15.4)	21 (26.9)
PP Criterion ² - Yes	77 (98.7)	75 (96.2)	72 (92.3)	71 (91.0)	68 (87.2)
No	1 (1.3)	2 (2.6)	5 (6.4)	6 (7.7)	10 (12.8)
Discontinued ³	0	1 (1.3)	1 (1.3)	1 (1.3)	0
mCC Arm - N	42	42	42	42	42
Exclusive product use ¹ - Yes	42 (100.0)	41 (97.6)	41 (97.6)	41 (97.6)	41 (97.6)
No	0	0	0	0	1 (2.4)
Discontinued ³	0	1 (2.4)	1 (2.4)	1 (2.4)	0
SA Arm - N	40	40	40	40	40
Abstinent ¹ - Yes	39 (97.5)	38 (95.0)	38 (95.0)	37 (92.5)	37 (92.5)
No	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)	3 (7.5)
PP Criterion ² - Yes	39 (97.5)	39 (97.5)	38 (95.0)	37 (92.5)	37 (92.5)
No	1 (2.5)	0	1 (2.5)	1 (2.5)	3 (7.5)
Discontinued ³	0	1 (2.5)	1 (2.5)	2 (5.0)	0

Abbreviations: CC = conventional cigarette; CO = carbon monoxide; FAS = Full Analysis Set; mCC = conventional cigarette; Max = maximum; Min = minimum; NRT = nicotine replacement therapy; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

[1] Subject in PP Set with no use of any nicotine or tobacco-containing product other than the assigned product. However, in the SA arm, NRT use was allowed during the study. In the SA arm, 100% abstinence also required CO breath test ≤ 10 ppm (apart from on Day 1).

[2] No use of more than 2 CC during a single day within any time period and no use of on average more than 0.5 CC per day over the exposure study.

[3] Discontinued in previous period, for each period.

Ambulatory Periods defined as Period 2 ([Day 6 Ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Percentages are based on the number of subjects (N) in the FAS for each arm and period.

Data Source: [Appendix 15, Tables 15.2.5.2.](#)

**Table 36 Summary of Product Use by Product Use Category in the Ambulatory Period - FAS**

Study Arm	Product Use Category	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)	Ambulatory Safety n (%)
THS m2.2 Arm (N=78)	THS m2.2 ([70-100]%)	71 (91.0)	69 (88.5)	68 (87.2)	71 (91.0)
	Primarily THS m2.2 ([95-100]%)	71 (91.0)	69 (88.5)	67 (85.9)	71 (91.0)
	Exclusively THS m2.2 (100%)	64 (82.1)	66 (84.6)	66 (84.6)	62 (79.5)
	Predominantly THS m2.2 ([70-95]%)	0	0	1 (1.3)	0
	Dual ([30-70]%)	0	2 (2.6)	2 (2.6)	0
	Dual mostly THS m2.2 ([60-70]%)	0	0	0	0
	Dual balanced ([40-60]%)	0	2 (2.6)	2 (2.6)	0
	Dual mostly CC ([30-40]%)	0	0	0	0
	CC ([0-30]%)	2 (2.6)	2 (2.6)	3 (3.8)	0
	Predominantly CC ([5-30]%)	0	0	1 (1.3)	0
	Primarily CC ([0-5]%)	2 (2.6)	2 (2.6)	2 (2.6)	0
	Exclusively CC (0%)	1 (1.3)	1 (1.3)	1 (1.3)	0
	Not Abstinent	4 (5.1)	4 (5.1)	4 (5.1)	5 (6.4)
	Missing	0	0	0	1 (1.3)
	Discontinued in previous period	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
mCC Arm (N=42)	CC Only (Exclusively CC)	41 (97.6)	41 (97.6)	41 (97.6)	41 (97.6)
	Discontinued in previous period	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)
SA Arm (N=40)	Abstinent	38 (95.0)	38 (95.0)	37 (92.5)	38 (95.0)
	Predominantly Abstinent	1 (2.5)	0	0	1 (2.5)
	Not Abstinent	0	1 (2.5)	1 (2.5)	0
	Discontinued in previous period	1 (2.5)	1 (2.5)	2 (5.0)	1 (2.5)

Abbreviations: CC = conventional cigarette; FAS = Full Analysis Set; mCC = conventional cigarette; SA = smoking abstinence;

THS m2.2 = Tobacco Heating System 2.2 Menthol.

Note: Ambulatory Periods defined as Period 2 ([Day 6 Ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]). Percentages are based on the number of subjects (N) in the FAS for each arm and period. Product use categories for Period 2, 3, and 4 were derived using rules for non-safety analysis. Ambulatory safety product use categories were derived using rules for safety analysis.

Data Source: [Appendix 15, Tables 15.2.2.4.](#)



11 ENDPOINT EVALUATIONS AND ADDITIONAL ANALYSES

11.1 Analysis of Biomarkers of Exposure for the Primary Objective

The primary endpoint variables for this study were assessed in a confinement setting on Day 5 for the BoExp COHb in blood in the evening between 08:00 to 09:30 PM (% saturation of hemoglobin) and in 24-hour urine for the following BoExp all expressed in concentration adjusted for creatinine: MHBMA, 3-HPMA, and S-PMA. The primary analysis endpoint variable for this study in an ambulatory setting was Total NNAL measured in 24-hour urine and expressed as concentration adjusted for creatinine on Day 90.

The figures, summaries, and analyses were performed on the PP Set. The figures and summaries were also repeated for the FAS. As a sensitivity analysis, the statistical analysis on the PP Set was repeated with a mixed model approach. In addition, as a further sensitivity analysis, the figures, summaries, and analyses were performed on the Compliant Population; a subset of the PP Set for subjects from the THS 2.2 Menthol arm who were exclusive THS 2.2 Menthol users or subjects from the mCC arm who were exclusive users of mCC, or subjects from the SA arm who were abstinent (note that NRT products could be used by the subjects in the SA arm as allowed by the protocol). However, for the Confinement Period (Period 1), the number of subjects in the Compliant Population was the same as for the PP Set, and thus, data has only been presented for the PP Set for the primary analysis in the Confinement Period in the CSR.

To assist with the interpretation, the profiles of the primary endpoints for the SA arm are included with those of the THS 2.2 Menthol and mCC arms, and are described in the primary endpoint section. The statistical analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL versus SA arm is described in [Section 11.2.1](#).

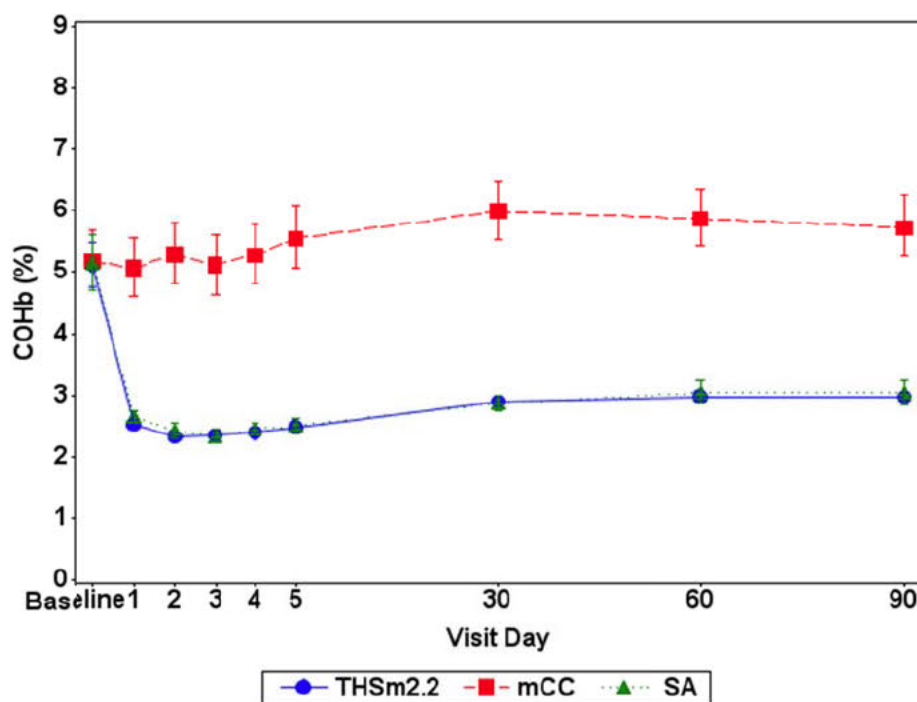
11.1.1 Carboxyhemoglobin in Whole Blood (% of Saturation of Hemoglobin) on Day 5 (Confinement Period)

Subject listings of COHb data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of COHb assessment data during the course of the study are provided in [Appendix 15, Table 15.2.4.1.1](#), [Table 15.2.4.1.2](#), and [Table 15.2.4.1.3](#) for the PP Set, FAS, and the Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.1.1.1](#) and [Table 15.2.4.1.1.2](#), respectively. Geometric mean and 95% CIs for evening COHb are presented graphically in [Appendix 15, Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, the Compliant Population, and the FAS, respectively. Data for the PP Set are also presented in [Figure 4](#).



Figure 4 Geometric Mean and 95% CI COHb in Whole Blood (%) during the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; COHb = carboxyhemoglobin; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

[Table 37](#) presents the results of the COHb assessments at each time point in the Confinement Period by study arm.

**Table 37 COHb in Whole Blood (%) Assessments by Study Arm During the Confinement Period (PP Set)**

Study Arm	Visit	Number of Subjects	Geometric CV*		Min	Median	Max
			Mean	(%)			
THS m2.2	Baseline	76	5.11	31.74	2.1	5.10	9.7
	Day 1	76	2.52	13.28	1.7	2.60	3.4
	Day 2	76	2.33	13.37	1.6	2.35	3.1
	Day 3	76	2.34	13.69	1.4	2.40	3.1
	Day 4	76	2.39	14.49	1.5	2.45	3.1
	Day 5, 15 min < T ₀	76	2.57	11.75	1.9	2.60	3.2
	Day 5, 12:00-01:30 PM	76	2.62	12.58	1.6	2.70	3.3
	Day 5, 04:00-05:30 PM	76	2.50	15.52	1.2	2.60	3.3
	Day 5, 08:00-09:30 PM	76	2.48	14.16	1.4	2.50	3.2
mCC	Baseline	42	5.17	31.51	2.4	5.40	10.3
	Day 1	42	5.06	31.18	2.8	5.10	10.0
	Day 2	42	5.29	30.85	2.9	5.15	9.0
	Day 3	42	5.11	31.02	2.9	4.95	9.4
	Day 4	42	5.28	30.20	2.5	5.50	9.7
	Day 5, 15 min < T ₀	41	3.97	21.54	2.6	4.00	6.5
	Day 5, 12:00-01:30 PM	41	5.19	30.87	2.7	5.00	10.4
	Day 5, 04:00-05:30 PM	41	5.33	30.90	2.4	5.10	10.4
	Day 5, 08:00-09:30 PM	42	5.55	29.83	2.7	5.65	9.5
SA	Baseline	39	5.15	27.16	3.1	5.10	8.3
	Day 1	39	2.65	11.84	1.9	2.70	3.4
	Day 2	39	2.42	15.35	1.9	2.40	4.6
	Day 3	39	2.33	13.22	1.8	2.30	3.0
	Day 4	39	2.44	11.00	1.9	2.50	3.1
	Day 5, 08:00-09:30 AM	39	2.66	12.65	1.9	2.70	3.2
	Day 5, 12:00-01:30 PM	39	2.57	12.55	2.0	2.60	3.3
	Day 5, 04:00-05:30 PM	39	2.54	13.34	2.0	2.50	3.4
	Day 5, 08:00-09:30 PM	39	2.50	15.50	1.7	2.40	3.4

Abbreviations: COHb = carboxyhemoglobin; CV = coefficient of variation; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

*geometric CV is presented

Data Source: [Appendix 15, Table 15.2.4.1.1](#).

The percent changes from baseline data during the course of the study are summarized in [Appendix 15, Table 15.2.4.1.1](#), [Table 15.2.4.1.2](#), and [Table 15.2.4.1.3](#) for the PP Set, FAS and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.1.1.1](#) and [Table 15.2.4.1.1.2](#), respectively.



Table 38 presents overall percentage of change from baseline in COHb evening assessment data in the Confinement Period by study arm.

Table 38 Percent Change from Baseline in COHb in Whole Blood (%) by Study Arm During the Confinement Period (PP Set)

Study Arm	Visit	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 1	76	-48.84	13.749	-73.3	-48.85	-14.8
	Day 2	76	-52.46	13.621	-78.4	-52.94	-18.5
	Day 3	76	-51.83	15.287	-78.4	-52.89	-4.8
	Day 4	76	-50.64	16.571	-77.5	-51.44	14.8
	Day 5, 15 min < T ₀	76	-47.29	16.120	-74.4	-47.50	4.8
	Day 5, 12:00-01:30 PM	76	-46.37	16.960	-73.3	-47.24	23.8
	Day 5, 04:00-05:30 PM	76	-48.89	15.541	-75.3	-50.00	-4.5
	Day 5, 08:00-09:30 PM	76	-49.24	15.099	-78.4	-49.53	-4.8
mCC	Day 1	42	-1.04	14.437	-35.5	1.04	25.7
	Day 2	42	3.59	16.859	-27.4	0.00	47.8
	Day 3	42	0.16	17.377	-32.9	0.00	39.4
	Day 4	42	3.24	15.964	-29.6	2.39	36.4
	Day 5, 15 min < T ₀	41	-21.69	14.913	-44.4	-22.22	17.2
	Day 5, 12:00-01:30 PM	41	2.75	20.604	-38.4	6.82	44.4
	Day 5, 04:00-05:30 PM	41	4.50	15.975	-26.0	4.65	35.1
	Day 5, 08:00-09:30 PM	42	8.90	18.963	-32.9	7.05	51.9
SA	Day 1	39	-47.06	13.210	-65.8	-48.89	-15.6
	Day 2	39	-50.90	15.369	-72.4	-55.17	-8.8
	Day 3	39	-52.98	13.315	-73.4	-54.10	-11.8
	Day 4	39	-50.75	13.378	-75.3	-53.85	-14.7
	Day 5, 08:00-09:30 AM	39	-46.40	15.295	-67.9	-47.92	-8.8
	Day 5, 12:00-01:30 PM	39	-47.81	16.267	-71.6	-51.06	-2.9
	Day 5, 04:00-05:30 PM	39	-48.34	16.224	-71.6	-51.22	-2.9
	Day 5, 08:00-09:30 PM	39	-49.11	16.379	-70.4	-53.66	-8.8

Abbreviations: COHb = carboxyhemoglobin; Max = maximum; mCC = menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

% change from baseline, where baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.1.1](#).

The profile of the mean evening COHb in the THS 2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Day 1, before plateauing during the Confinement Period.

Geometric mean COHb values decreased in the THS 2.2 Menthol arm from baseline (5.11%) to Day 5 (2.48%) in contrast to COHb values in the mCC arm, which remained similar at baseline (5.17%) and Day 5 (5.55%). These values corresponded to percent



changes from baseline of -49.24% and 8.90% for the THS 2.2 Menthol and mCC arms, respectively, with the majority of the decrease from baseline in the THS 2.2 Menthol arm achieved by Day 1 (-48.84%). In the SA arm, geometric mean COHb values decreased from baseline (5.15%) to Day 5 (2.50%), as expected, which corresponded to a -49.11% change from baseline, with the majority of the decrease observed on Day 1.

There were no apparent differences in COHb levels between male and female subjects for any study arm at baseline or during the Confinement Period. At baseline in the THS 2.2 Menthol arm, there were higher mean COHb levels in blood for subject who smoked >19 cigarettes/day compared to subjects who smoked 10-19 cigarettes/day, with means of 5.69% (95% CI: 5.14, 6.30) and 4.61% (95% CI: 4.20, 5.06), respectively. On Days 1, 2, and 3, there were higher mean percentage decreases from baseline in subjects who smoked >19 cigarettes/day, with means of -53.86% (95% CI: -57.91, -49.82), 56.97% (95% CI: -61.11, -52.82), and -56.59% (95% CI: -61.16, -52.02), respectively, compared to those who smoked 10-19 cigarettes/day, with means of -44.08% (95% CI: -48.51, -39.65), -48.19% (95% CI: -52.56, -43.82), and -47.32% (95% CI: -52.35, -42.28).

Analysis of evening blood COHb (%) for THS 2.2 Menthol users versus mCC on Day 5 is tabulated in [Appendix 15, Table 15.2.3.1.1](#) and [Table 15.2.3.1.3](#) for the PP Set and Compliant Population, respectively. Data for the PP Set is also provided in [Table 39](#).

Table 39 Analysis of Evening Blood COHb (%) versus mCC on Day 5 (PP Set)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean		CV (%)	95% CI	p-value
			Ratio (THS m2.2:mCC) (%)				
THS m2.2	76	2.47	44.94		17.24	42.11, 47.97	< .001
mCC	42	5.49					

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; COHb = carboxyhemoglobin; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. P-value is for the one-sided test for comparison between THS m2.2 and mCC.

Data Source: [Appendix 15, Table 15.2.3.1.1](#).

On Day 5 (evening), the LS mean of COHb in subjects who switched to THS 2.2 Menthol use was 55.06% lower than that of subjects who continued to smoke mCC (95% CI: 52.03, 57.89; p-value <0.001).

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.1.2](#)), with the LS mean of COHb in subjects who



switched to THS 2.2 Menthol 55.07% lower than that of subjects who continued to smoke mCC (95% CI: 52.01, 57.94; p-value < 0.001).

These analysis results for the COHb assessment were consistent with the study hypothesis, as the geometric mean levels were lower in the THS 2.2 Menthol arm compared to the mCC arm (55.06% reduction).

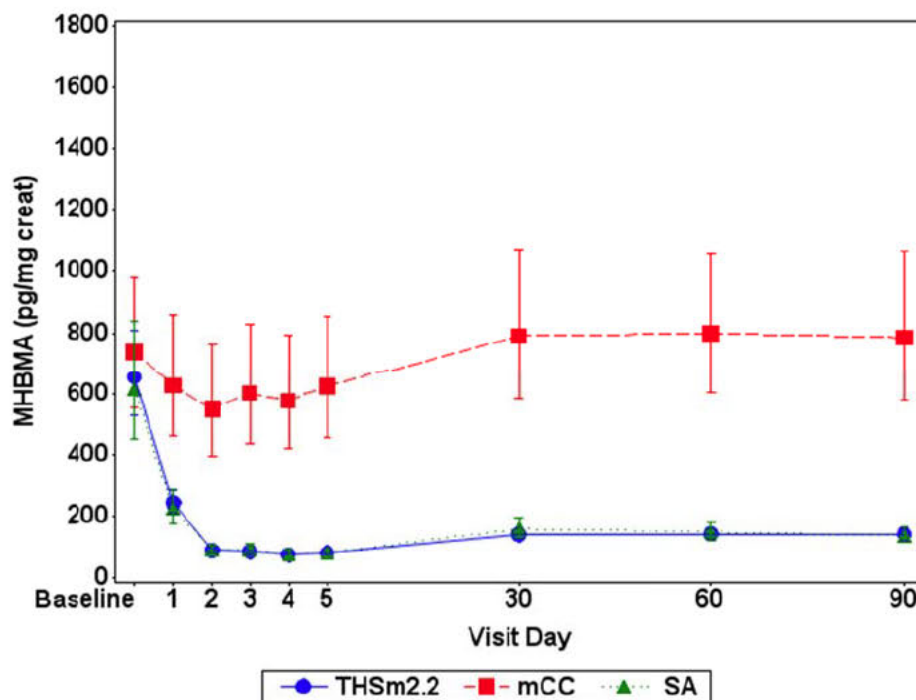
11.1.2 Monohydroxybutenyl Mercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 5 (Confinement Period)

Subject listings of MHBMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of MHBMA concentration adjusted for creatinine data during the course of the study are provided in [Appendix 15, Table 15.2.4.2.1](#), [Table 15.2.4.2.2](#), and [Table 15.2.4.2.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.2.1.1](#), and [Table 15.2.4.2.1.2](#), respectively. Geometric mean and 95% CIs for MHBMA are presented graphically in [Appendix 15, Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, Compliant Population, and FAS, respectively. Data for the PP Set are also provided in [Figure 5](#).



Figure 5 Geometric Mean and 95% CI MHBMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mCC = menthol conventional cigarette; MHBMA = monohydroxybutenyl mercapturic acid; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

[Table 40](#) presents the results of the MHBMA concentrations adjusted for creatinine in the Confinement Period by study arm.



Table 40 Absolute Values of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm in the Confinement Period (PP Set)

Study Arm	Visit	Number of Geometric		CV* (%)	Min	Median	Max
		Subjects	Mean				
THS m2.2	Baseline	76	653.78	115.03	80.8	708.14	4067.8
	Day 1	76	242.57	77.20	64.9	278.15	1279.8
	Day 2	76	87.99	39.48	36.2	91.49	211.1
	Day 3	76	84.53	37.97	40.7	86.06	194.8
	Day 4	76	73.84	42.90	31.3	77.00	173.8
	Day 5	76	81.71	35.50	27.3	81.39	150.6
mCC	Baseline	42	737.29	114.14	145.8	756.44	3506.2
	Day 1	42	627.24	131.96	77.2	584.28	4339.6
	Day 2	42	548.51	143.67	46.3	606.21	4273.4
	Day 3	42	600.28	138.60	64.2	590.79	4277.4
	Day 4	42	577.44	133.52	96.6	533.59	3256.8
	Day 5	42	622.58	132.98	109.2	607.12	3901.1
SA	Baseline	39	614.87	122.18	139.2	562.84	2896.8
	Day 1	39	223.52	94.27	31.3	223.05	928.1
	Day 2	39	90.66	56.16	33.3	87.10	390.0
	Day 3	39	91.77	53.73	30.7	86.21	370.7
	Day 4	39	76.57	51.10	30.5	76.10	242.7
	Day 5	39	80.72	41.57	30.7	81.43	202.4

Abbreviations: CV = coefficient of variation; Max = maximum; mCC = conventional cigarette;

Min = minimum; MHBMA = monohydroxybutenyl mercapturic acid; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms or last assessment prior to 10:00 AM in SA arm on Day 1.

*geometric CV is presented

Data Source: [Appendix 15, Table 15.2.4.2.1](#).

The percent changes from baseline for MHBMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.4.2.1](#), [Table 15.2.4.2.2](#), and [Table 15.2.4.2.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.2.1.1](#) and [Table 15.2.4.2.1.2](#), respectively.

[Table 41](#) presents overall percentage of change from baseline in MHBMA concentration adjusted for creatinine in the Confinement Period by study arm.



Table 41 Percent Change from Baseline MHBMA Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm During the Confinement Period (PP Set)

Study Arm	Visit	Number of Arithmetic		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 1	76	-54.07	51.809	-89.8	-64.51	358.2
	Day 2	76	-81.66	17.001	-97.7	-87.24	18.4
	Day 3	76	-81.27	19.898	-97.6	-88.23	51.0
	Day 4	76	-82.66	19.461	-97.9	-88.84	43.0
	Day 5	76	-80.54	20.866	-98.3	-86.85	37.3
mCC	Day 1	42	-12.50	19.733	-62.2	-9.79	43.1
	Day 2	42	-21.90	23.798	-72.0	-25.66	44.6
	Day 3	42	-13.24	32.462	-68.5	-17.61	105.6
	Day 4	42	-18.58	22.615	-59.2	-20.43	33.9
	Day 5	42	-11.98	28.782	-53.6	-17.42	113.6
SA	Day 1	39	-59.26	21.430	-85.7	-66.27	9.1
	Day 2	39	-77.96	19.758	-97.1	-84.24	-13.1
	Day 3	39	-75.27	24.600	-97.2	-87.04	-2.2
	Day 4	39	-80.77	16.651	-97.9	-86.57	-36.8
	Day 5	39	-78.67	18.978	-98.1	-86.78	-35.9

Abbreviations: Max = maximum; mCC = conventional cigarette; Min = minimum; MHBMA = monohydroxybutenyl mercapturic acid; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

% change from baseline, where baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.2.1](#).

The profile of the mean MHBMA urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was comparable to that of the SA arm during the Confinement Period, with a sharp decline on Day 1 and a further decrease observed on Day 2, before plateauing during the Confinement Period.

Geometric mean MHBMA values decreased in the THS 2.2 Menthol arm from baseline (653.78 pg/mg creat) to Day 5 (81.71 pg/mg creat) in contrast to MHBMA values in the mCC, which remained similar at baseline (737.29 pg/mg creat) and Day 5 (622.58 pg/mg creat). These values corresponded to percent changes from baseline of -80.54% and -11.98% for the THS 2.2 Menthol and mCC arms, respectively, with the majority of the decrease from baseline in the THS 2.2 Menthol arm achieved by Day 2 (81.66%). In the SA arm, geometric mean MHBMA values decreased from baseline (614.87 pg/mg creat) to Day 5 (80.72 pg/mg creat), as expected, which corresponded to a -78.67% change from baseline, with the majority of the decrease observed by Day 2.

There were no apparent differences in MHBMA levels based on sex for any study arm at baseline or during the Confinement Period.



In addition, in the THS 2.2 Menthol arm there were higher levels of MHBMA for subjects who smoked >19 cigarettes/day compared to subjects who smoked 10-19 cigarettes/day at baseline, with geometric means of 965.87 (95% CI: 740.30, 1260.18) and 451.47 (95% CI: 339.58, 600.22), respectively. During the Confinement Period, however, there were no apparent differences in mean MHBMA levels between the 2 cigarette consumption categories.

Analysis of MHBMA urinary concentrations adjusted for creatinine for THS 2.2 Menthol users versus mCC on Day 5 is tabulated in [Appendix 15, Table 15.2.3.1.1](#) and [Table 15.2.3.1.3](#) for the PP Set and Compliant Population, respectively. Data for the PP Set is also provided in [Table 42](#).

Table 42 Analysis of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus mCC on Day 5 (PP Set)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)		CV (%)	95% CI	p-value
THS m2.2	76	83.21	13.49		58.68	10.96, 16.60	< .001
mCC	42	617.04					

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; MHBMA = Monohydroxybutenyl mercapturic acid; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. P-value is for the one-sided test for comparison between THS m2.2 and mCC.

Data Source: [Appendix 15, Table 15.2.3.1.1](#).

On Day 5, the LS mean of MHBMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 86.51% lower than that of subjects who continued to smoke mCC (95% CI: 83.40, 89.04; p-value <0.001).

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.1.2](#)), with the LS mean of MHBMA in subjects who switched to THS 2.2 Menthol 86.66% lower than that of subjects who continued to smoke mCC (95% CI: 83.54, 89.18; p-value <0.001).

These analysis results for MHBMA urinary concentration adjusted for creatinine were consistent with the study hypothesis, as the geometric mean levels were lower in the THS 2.2 Menthol arm compared to the mCC arm (86.51% reduction).

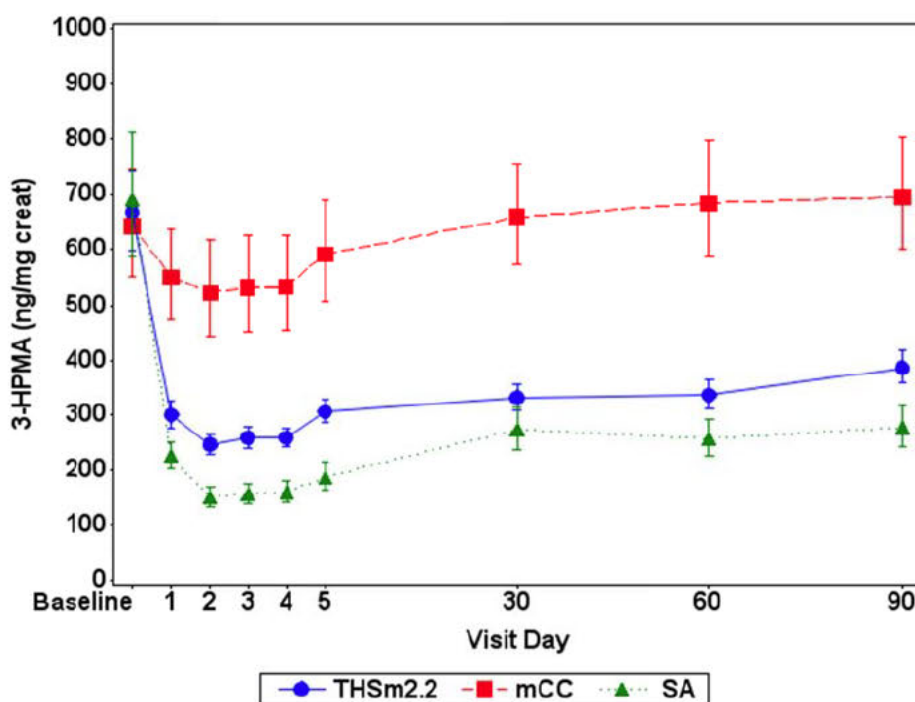
11.1.3 3-hydroxypropylmercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 5 (Confinement Period)

Subject listings of 3-HPMA data are provided in [Appendix 15, Listing 15.3.3.1](#).



Descriptive statistics of 3-HPMA concentration adjusted for creatinine data during the course of the study are provided in [Appendix 15, Table 15.2.4.3.1](#), [Table 15.2.4.3.2](#), and [Table 15.2.4.3.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.3.1.1](#), and [Table 15.2.4.3.1.2](#), respectively. Geometric mean and 95 % CIs for 3-HPMA are presented graphically in [Appendix 15, Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, Compliant Population, and FAS, respectively. Data for the PP Set are also presented in [Figure 6](#).

Figure 6 Geometric Mean and 95% CI 3-HPMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 3-HPMA = 3-hydroxypropylmethylcarbamoyl; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#)

[Table 43](#) presents the results of the 3-HPMA concentration; adjusted for creatinine in the Confinement Period by study arm.



Table 43 Absolute Values of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) by Study Arm in the Confinement Period (PP Set)

Study Arm	Visit	Number of Geometric		CV* (%)	Min	Median	Max
		Subjects	Mean				
THS m2.2	Baseline	76	667.53	49.95	264.9	681.14	2669.4
	Day 1	76	298.65	37.22	128.6	284.04	976.7
	Day 2	76	245.31	33.96	111.6	238.75	693.1
	Day 3	76	257.30	33.83	121.5	260.35	560.6
	Day 4	76	257.01	30.09	128.1	269.23	485.3
	Day 5	76	304.68	30.46	163.3	300.59	631.0
mCC	Baseline	42	642.20	51.11	253.0	617.49	2075.8
	Day 1	42	550.49	50.35	220.8	561.64	1684.5
	Day 2	42	522.67	57.68	176.1	526.22	1620.9
	Day 3	42	531.35	56.52	176.4	461.47	1917.1
	Day 4	42	533.66	54.34	165.4	471.41	1658.7
	Day 5	42	591.33	51.99	261.3	587.31	1548.8
SA	Baseline	39	691.14	53.57	273.3	660.55	1873.9
	Day 1	39	224.60	34.41	121.2	208.44	494.7
	Day 2	39	150.03	37.11	74.1	146.27	369.9
	Day 3	39	156.10	35.35	86.7	157.66	363.3
	Day 4	39	159.32	38.10	57.5	163.89	385.9
	Day 5	39	186.71	42.96	48.9	195.57	366.7

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CV = coefficient of variation; Max = maximum; mCC = conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms or last assessment prior to 10:00 AM in SA arm on Day 1.

*geometric CV is presented

Data Source: [Appendix 15, Table 15.2.4.3.1](#).

The percent changes from baseline for 3-HPMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.4.3.1](#), [Table 15.2.4.3.2](#), and [Table 15.2.4.3.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.3.1.1](#) and [Table 15.2.4.3.1.2](#), respectively.

[Table 44](#) presents overall percentage of change from baseline in 3-HPMA concentration adjusted for creatinine in the Confinement Period by study arm.



Table 44 Percent Change from Baseline 3-HPMA Concentration Adjusted for Creatinine (ng/mg creat) by Study Arm During the Confinement Period (PP Set)

Study Arm	Visit	Number of Arithmetic		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 1	76	-52.86	15.454	-80.4	-56.67	-6.0
	Day 2	76	-61.22	13.078	-81.3	-63.23	-14.1
	Day 3	76	-58.86	15.850	-80.6	-62.65	-0.3
	Day 4	76	-58.46	17.569	-83.6	-60.90	15.9
	Day 5	76	-50.90	19.081	-80.1	-54.84	15.5
mCC	Day 1	42	-11.99	20.433	-47.6	-13.14	41.4
	Day 2	42	-16.49	18.863	-54.0	-19.00	25.5
	Day 3	42	-14.57	21.622	-58.0	-17.76	35.3
	Day 4	42	-14.48	19.969	-61.5	-14.07	32.8
	Day 5	42	-5.48	21.382	-47.2	-5.10	48.3
SA	Day 1	39	-64.72	14.033	-89.2	-65.20	-25.5
	Day 2	39	-75.87	10.871	-93.1	-76.29	-48.3
	Day 3	39	-74.61	12.520	-91.5	-77.80	-44.0
	Day 4	39	-73.78	13.853	-89.9	-75.19	-21.9
	Day 5	39	-68.42	18.422	-92.1	-71.37	1.0

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; Max = maximum; mCC = conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.3.1.](#)

The profile of the mean 3-HPMA urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was similar to that of the SA arm, with the majority of the decrease occurring by Day 1 and plateauing from Day 2 onwards during the Confinement Period. However, the magnitude of the decrease observed in the THS 2.2 Menthol arm was not as great as that in the SA arm.

Geometric mean 3-HPMA values decreased in the THS 2.2 Menthol arm from baseline (667.53 ng/mg creat) to Day 5 (304.68 ng/mg creat) whereas 3-HPMA values in the mCC arm remained similar at baseline (642.20 ng/mg creat) and Day 5 (591.33 ng/mg creat). These values corresponded to percent changes from baseline of -50.90% and -5.48% for the THS 2.2 Menthol and mCC arms, respectively, with the majority of the decrease from baseline in the THS 2.2 Menthol arm achieved by Day 1 (-52.86%). In the SA arm, geometric mean 3-HPMA values decreased from baseline (691.14 ng/mg creat) to Day 5 (186.71 ng/mg creat), as expected, which corresponded to a -68.42% change from baseline, with the majority of the decrease observed by Day 1.

There were no apparent differences at baseline or during the Confinement Period in mean 3-HPMA levels between male and female subjects.



There was a higher mean level of 3-HPMA at baseline in subjects who smoked >19 cigarettes/day compared to subjects who smoked 10-19 cigarettes/day in the THS 2.2 Menthol arm, with means of 815.68 (95% CI: 711.73, 934.80) and 551.93 (95% CI: 476.57, 639.19), respectively. In addition, on Day 3 and 5 there were higher mean decreases from baseline for the subjects who smoked >19 cigarettes/day compared to those who smoked 10-19 cigarette/day, with mean percentage changes from baseline on Day 5 of -56.01% and -46.06%, respectively (95% CI of -61.69, -50.32 and -52.51, -39.62, respectively).

Analysis of 3-HPMA urinary concentrations adjusted for creatinine for THS 2.2 Menthol users versus mCC on Day 5 is tabulated in [Appendix 15, Table 15.2.3.1.1](#) and [Table 15.2.3.1.3](#) for the PP Set and Compliant Population, respectively. Data for the PP Set is also provided in [Table 45](#).

Table 45 Analysis of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) versus mCC on Day 5 (PP Set)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)		CV (%)	95% CI	p-value
THS m2.2	76	304.56	50.67		32.72	44.88, 57.20	< .001
mCC	42	601.11					

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = conventional cigarette; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. P-value is for the one-sided test for comparison between THS m2.2 and mCC.

Data Source: [Appendix 15, Table 15.2.3.1.1](#).

On Day 5, the LS mean of 3-HPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 49.33% lower than that of subjects who continued to smoke mCC (95% CI: 42.80, 55.12; p-value <0.001).

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.1.2](#)), with the LS mean of 3-HPMA in subjects who switched to THS 2.2 Menthol 48.68% lower than that of subjects who continued to smoke mCC (95% CI: 42.04, 54.56; p-value <0.001).

These analysis results were consistent with the study hypothesis, as the geometric mean levels were lower in the THS 2.2 Menthol arm compared to the mCC arm (49.33% reduction).

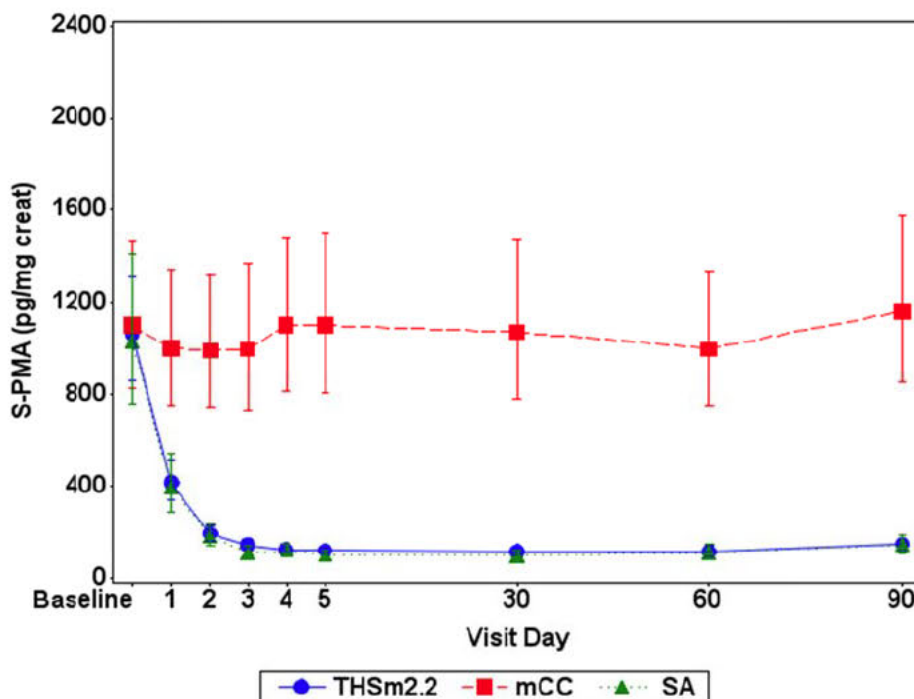


11.1.4 S-phenylmercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 5 (Confinement Period)

Subject listings of S-PMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of S-PMA concentration adjusted for creatinine data during the course of the study are provided in [Appendix 15, Table 15.2.4.4.1](#), [Table 15.2.4.4.2](#), and [Table 15.2.4.4.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.4.1.1](#), and [Table 15.2.4.4.1.2](#), respectively. Geometric mean and 95% CIs for S-PMA are presented graphically in [Appendix 15, Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, Compliant Population, and the FAS, respectively. Data for the PP Set was also provided in [Figure 7](#).

Figure 7 Geometric Mean and 95% CI S-PMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THSm2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.1.2](#).



Table 46 presents the results of the S-PMA concentrations adjusted for creatinine in the Confinement Period by study arm.

Table 46 Absolute Values of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm in the Confinement Period (PP Set)

Study Arm	Visit	Number of Geometric		CV* (%)	Min	Median	Max
		Subjects	Mean				
THS m2.2	Baseline	76	1058.84	115.52	167.6	1274.20	6057.5
	Day 1	76	415.85	112.05	85.5	475.21	1929.6
	Day 2	76	191.02	80.08	22.9	199.67	1151.6
	Day 3	76	143.55	59.90	47.5	149.34	538.3
	Day 4	76	122.57	45.94	55.9	121.18	359.2
	Day 5	76	118.36	44.66	51.5	119.32	280.7
mCC	Baseline	42	1096.79	115.64	206.8	1041.05	6078.8
	Day 1	42	998.20	119.69	191.4	852.83	6271.2
	Day 2	42	986.94	115.74	237.4	912.34	7352.9
	Day 3	42	994.67	132.30	158.0	888.01	7116.2
	Day 4	42	1095.90	122.17	151.5	1035.81	7710.4
	Day 5	42	1096.47	129.25	174.4	1103.64	7234.4
SA	Baseline	39	1027.37	123.71	190.4	902.99	5315.9
	Day 1	39	392.60	127.59	78.8	438.24	2127.0
	Day 2	39	181.50	88.35	44.7	159.82	832.8
	Day 3	39	108.40	97.62	17.1	113.53	455.9
	Day 4	39	118.06	67.55	18.3	105.74	325.7
	Day 5	39	102.51	62.05	21.4	106.75	279.9

Abbreviations: CV = coefficient of variation; Max = maximum; mCC = conventional cigarette;

Min = minimum; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

*geometric CV is presented

Data Source: [Appendix 15, Table 15.2.4.4.1](#).

The percent changes from baseline for S-PMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.4.4.1, Table 15.2.4.4.2, and Table 15.2.4.4.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.4.1.1 and Table 15.2.4.4.1.2](#), respectively.

Table 47 presents overall percentage of change from baseline in S-PMA concentration adjusted for creatinine data in the Confinement Period by study arm.



Table 47 Percent Change from Baseline S-PMA Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm During the Confinement Period (PP Set)

Study Arm	Visit	Number of Arithmetic		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 1	76	-58.31	15.368	-86.3	-61.48	5.9
	Day 2	76	-79.70	9.675	-98.2	-83.08	-55.1
	Day 3	76	-84.17	9.905	-95.5	-87.61	-40.5
	Day 4	76	-85.76	10.105	-96.4	-89.45	-46.0
	Day 5	76	-85.88	10.628	-97.5	-89.85	-41.6
mCC	Day 1	42	-7.39	17.447	-43.5	-8.64	36.0
	Day 2	42	-7.27	21.626	-60.2	-5.63	41.9
	Day 3	42	-5.46	26.804	-56.1	-5.15	54.4
	Day 4	42	6.63	47.495	-45.0	-2.09	247.8
	Day 5	42	5.44	35.808	-47.8	1.42	100.9
SA	Day 1	39	-60.17	11.141	-84.1	-60.17	-36.1
	Day 2	39	-80.53	9.044	-92.6	-82.69	-58.5
	Day 3	39	-87.72	7.860	-97.3	-89.98	-53.2
	Day 4	39	-86.28	8.620	-95.5	-89.89	-63.0
	Day 5	39	-86.80	10.811	-98.1	-90.78	-45.0

Abbreviations: Max = maximum; mCC = conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.4.1](#).

The profile of the mean S-PMA urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was similar to that of the SA arm, with an initial decrease on Day 1 and a maximum decrease observed by Day 5.

Geometric mean S-PMA values decreased in the THS 2.2 Menthol arm from baseline (1058.84 pg/mg creat) to Day 5 (118.36 pg/mg creat), whereas S-PMA values in the mCC arm remained similar at baseline (1096.79 pg/mg creat) and Day 5 (1096.47 pg/mg creat). These values correspond to percent changes from baseline of -85.88% and 5.44% for the THS 2.2 Menthol and mCC arms, respectively, with the majority of the decrease from baseline in the THS 2.2 Menthol arm achieved by Day 1. In the SA arm, geometric mean S-PMA values decreased from baseline (1027.37 pg/mg creat) to Day 5 (102.51 pg/mg creat), as expected, which corresponded to a -86.80% change from baseline, with the majority of the decrease achieved by Day 1.

There were no apparent differences in mean S-PMA levels between male and female subjects at baseline or during the Confinement Period for any study arm. There was no apparent differences in mean S-PMA levels between subjects who smoked 10-19 cigarettes/day and subjects who smoked >19 cigarettes/day at baseline for any



study arm. During the Confinement Period on Day 5 there was a greater mean percentage decrease from baseline for S-PMA in the THS 2.2 Menthol arm for subjects who smoked >19 cigarettes/day at baseline compared to subjects who smoked 10-19 cigarettes/day at baseline, with means of -89.30% (95% CI: -92.10, -86.51) and -82.63% (95% CI: -86.39, -78.87).

Analysis of S-PMA urinary concentrations adjusted for creatinine for THS 2.2 Menthol users versus mCC on Day 5 is tabulated in [Appendix 15, Table 15.2.3.1.1](#) and [Table 15.2.3.1.3](#) for the PP Set and Compliant Population, respectively. Data for the PP Set is also provided in [Table 48](#).

Table 48 Analysis of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus mCC on Day 5 (PP Set)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		CV (%)	95% CI	p-value
			(THS m2.2:mCC) (%)				
THS m2.2	76	119.18	10.97		46.63	9.26, 12.99	< .001
mCC	42	1086.89					

Abbreviations: ANCOVA = analysis of covariance analysis; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an analysis of covariance (ANCOVA) model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. P-value is for the one-sided test for comparison between THS m2.2 and mCC.

Data Source: [Appendix 15, Table 15.2.3.1.1](#).

On Day 5, the LS mean of S-PMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 89.03% lower than that of subjects who continued to smoke mCC (95% CI: 87.01, 90.74; p-value <0.001).

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.1.2](#)), with the LS mean of S-PMA in subjects who switched to THS 2.2 Menthol 89.16% lower than that of subjects who continued to smoke mCC (95% CI: 87.15, 90.86; p-value <0.001).

These analysis results for S-PMA urinary concentration adjusted for creatinine were consistent with the study hypothesis, as the geometric mean levels were lower in the THS 2.2 Menthol arm compared to the mCC arm (89.03% reduction).

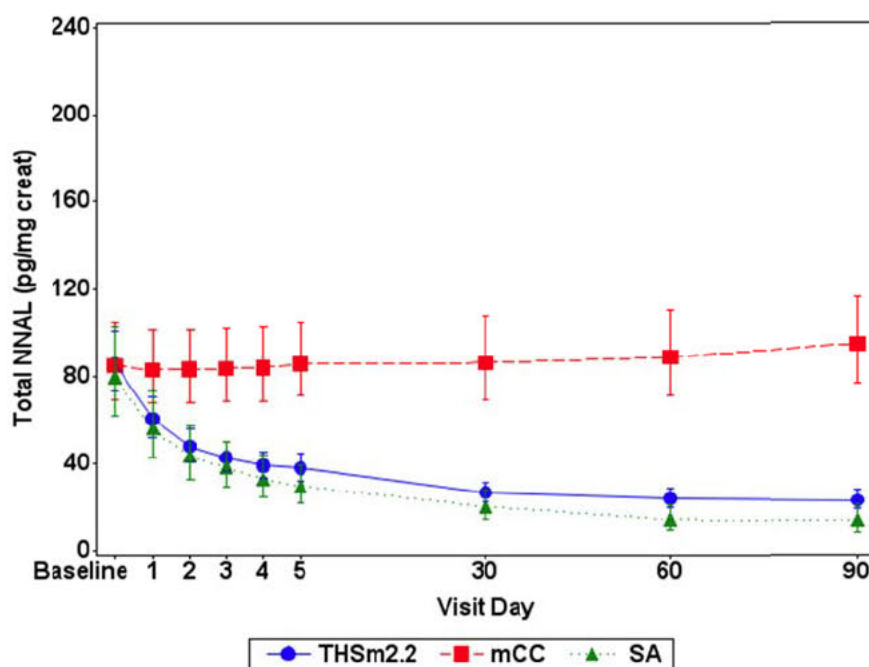
11.1.5 Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 90 (Ambulatory Period)

Subject listings of Total NNAL data are provided in [Appendix 15, Listing 15.3.3.1](#).



Descriptive statistics of Total NNAL concentration adjusted for creatinine data during the course of the study are provided in [Appendix 15, Table 15.2.4.5.1](#), [Table 15.2.4.5.2](#), and [Table 15.2.4.5.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.5.1.1](#) and [Table 15.2.4.5.1.2](#), respectively. Geometric mean and 95% CIs for Total NNAL are presented graphically in [Appendix 15, Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, Compliant Population, and the FAS, respectively and presented in [Figure 8](#).

Figure 8 Geometric Mean and 95% CI Total NNAL Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mCC = menthol conventional cigarette; NNA_L = 4 [methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.
Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.
Baseline is summarized using the baseline data from the PP Set for Period 1.
Data Source: [Appendix 15, Figure 15.1.1.2](#).

[Table 49](#) presents the results of the Total NNAL concentrations adjusted for creatinine following the Ambulatory Period by study arm.



Table 49 Absolute Values of Total NNAL Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm on Day 90 (Ambulatory Period) (PP Set)

Study Arm	Visit	Number of Geometric		CV* (%)	Min	Median	Max
		Subjects	Mean				
THS m2.2	Baseline	70	90.66	74.30	15.9	107.17	342.9
	Day 90	70	23.23	89.70	3.5	25.28	158.0
mCC	Baseline	41	85.55	75.52	17.0	88.74	318.8
	Day 90	41	95.03	73.04	22.4	111.87	284.5
SA	Baseline	37	78.79	94.45	11.0	84.24	376.4
	Day 90	37	13.95	214.03	1.0	12.93	166.1

Abbreviations: CV = coefficient of variation; Max = maximum; mCC = menthol conventional cigarette;

Min = minimum; NNAL = 4 [methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

*geometric CV is presented

Data Source: [Appendix 15, Table 15.2.4.5.1](#).

The percent changes from baseline for Total NNAL concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.4.5.1](#), [Table 15.2.4.5.2](#), and [Table 15.2.4.5.3](#) for the PP Set, FAS, and Compliant Population, respectively. The descriptive statistics of the PP Set are further summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.4.5.1.1](#) and [Table 15.2.4.5.1.2](#), respectively.

[Table 50](#) presents overall percentage of change from baseline in Total NNAL concentration adjusted for creatinine data.



Table 50 **Percent Change from Baseline Total NNAL Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm on Day 90 (Ambulatory Period) (PP Set)**

Study Arm	Visit	Number of Arithmetic		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 90	70	-68.58	21.270	-93.3	-73.80	6.2
mCC	Day 90	41	18.79	41.869	-60.3	21.57	117.4
SA	Day 90	37	-66.54	35.413	-97.6	-79.34	10.5

Abbreviations: Max = maximum; mCC = menthol conventional cigarette; Min = minimum; NNAL = 4 [methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.5.1](#).

The profile of the mean Total NNAL urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was comparable to that of the SA arm, with a gradual decrease from Day 1 to Day 90.

Geometric mean Total NNAL values decreased in the THS 2.2 Menthol arm from baseline (90.66 pg/mg creat) to Day 90 (23.23 pg/mg creat), whereas Total NNAL values in the mCC arm remained similar at baseline (85.55 pg/mg creat) and Day 90 (95.03 pg/mg creat). These values corresponded to percent changes from baseline of -68.58% and 18.79% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total NNAL values decreased from baseline (78.79 pg/mg creat) to Day 90 (13.95 pg/mg creat), as expected, which corresponded to a -66.54% change from baseline.

There were no apparent differences in mean levels of Total NNAL at baseline or during the Ambulatory Period between male and female subjects and between subjects who smoked 10-19 cigarettes/day and subjects who smoked >19 cigarettes/day.

Analysis of Total NNAL urinary concentrations adjusted for creatinine for THS 2.2 Menthol users versus mCC on Day 90 is tabulated in [Appendix 15, Table 15.2.3.1.1](#) and [Table 15.2.3.1.3](#) for the PP Set and Compliant Population, respectively. Data is also provided in [Table 51](#).

**Table 51 Analysis of Total NNAL Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus mCC on Day 90 (PP Set and Compliant Population)**

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		CV (%)	95% CI	p-value
			(THS m2.2:mCC) (%)				
PP Set							
THS m2.2	70	22.48	23.25		86.42	17.38, 31.11	< .001
mCC	41	96.65					
Compliant Population							
THS m2.2	65	21.89	22.60		85.85	16.85, 30.32	< .001
mCC	41	96.86					

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; NNAL = 4 [methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. Data Source: [Appendix 15, Table 15.2.3.1.1](#) and [Table 15.2.3.1.3](#).

On Day 90, the LS mean of Total NNAL urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 76.75% lower than that of subjects who continued to smoke mCC (95% CI: 68.89, 82.62; p-value <0.001) within the PP Set.

An additional sensitivity analysis using a mixed model approach showed consistent results on Day 90 ([Appendix 15, Table 15.2.3.1.2](#)), with the LS mean of Total NNAL in subjects who switched to THS 2.2 Menthol 76.80% lower than that of subjects who continued to smoke mCC (95% CI: 68.9, 82.69; p-value <0.001). In addition, analysis of Total NNAL on Day 90 for the Compliant Population was consistent with the results of the PP Set, with the LS mean of Total NNAL in subjects who switched to THS 2.2 Menthol use 77.40% lower than that of subjects who continued to smoke mCC (95% CI: 69.68, 83.15; p-value <0.001).

These analysis results for Total NNAL urinary concentration adjusted for creatinine were consistent with the study hypothesis, as the geometric mean levels were lower in the THS 2.2 Menthol arm compared to the mCC arm (76.75% reduction) on Day 90.

11.2 Analysis of Secondary Objectives/Endpoints

All endpoint variables for this study were studied in a confinement setting and an ambulatory setting as part of a secondary endpoint/objective analysis in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke



mCC and compared to SA. The endpoint variables that were part of the primary objective are discussed in [Section 11.1](#) for the Confinement Period and in [Section 11.2.1](#) and [11.2.2](#) for the Ambulatory Period.

The figures, summaries, and analyses were performed on the PP Set. The figures and summaries were also repeated for the FAS. As a sensitivity analysis for the BoExp, the statistical analysis on the PP Set was repeated with a mixed model approach. In addition, as a further sensitivity analysis for the BoExp, the figures, summaries, and analyses were performed on the Compliant Population; a subset of the PP Set for subjects from the THS 2.2 Menthol arm who were exclusive THS 2.2 Menthol users or subjects from the mCC arm who were exclusive users of mCC, or subjects from the SA arm who are abstinent. As the number of subjects in the Compliant Population was the same as the PP Set Period 1, only data of the PP Set Period 1 has been presented for the Confinement Period. For the Ambulatory Periods, the Compliant Populations differed from the PP Set, so both data sets were taken into account in the analyses.

11.2.1 Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL During the Study

11.2.1.1 Carboxyhemoglobin in Whole Blood (% of Saturation of Hemoglobin) During the Ambulatory Period

Subject listings and descriptive statistics of COHb assessment are provided as described in [Section 11.1.1](#). Geometric mean and 95% CIs for COHb throughout the study are presented graphically in [Appendix 15](#), [Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, Compliant Population, and FAS, respectively. Data for the PP Set are presented in [Figure 4](#).

[Table 52](#) presents the results of the COHb assessments at each time point in the Ambulatory Period by study arm.

**Table 52 COHb in Whole Blood (%) Assessments by Study Arm During the Ambulatory Period (PP Set)**

Study Arm	Visit	Number of		Geometric CV*		Min	Median	Max
		Subjects	Mean	(%)				
THS m2.2	Baseline	76	5.11	31.74	2.1	5.10	9.7	
	Day 5	76	2.48	14.16	1.4	2.50	3.2	
	Day 30	74	2.89	13.18	2.1	3.00	4.2	
	Day 60	71	2.98	13.36	2.3	2.90	5.6	
	Day 90	70	2.97	12.22	2.4	2.90	4.3	
mCC	Baseline	42	5.17	31.51	2.4	5.40	10.3	
	Day 5	42	5.55	29.83	2.7	5.65	9.5	
	Day 30	41	6.00	25.33	3.7	6.10	11.4	
	Day 60	41	5.87	25.59	3.3	6.10	11.8	
	Day 90	41	5.73	28.18	3.2	6.00	11.9	
SA	Baseline	39	5.15	27.16	3.1	5.10	8.3	
	Day 5	39	2.50	15.50	1.7	2.40	3.4	
	Day 30	39	2.87	12.34	2.2	2.90	3.4	
	Day 60	38	3.04	18.43	2.3	2.95	5.3	
	Day 90	37	3.04	20.22	2.2	2.90	5.3	

Abbreviations: COHb = carboxyhemoglobin; CV = coefficient of variation; PP = per protocol; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS 2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

*geometric CV is presented

Data Source: [Appendix 15, Table 15.2.4.1.1.](#)

[Table 53](#) presents overall percentage change from baseline in COHb assessment data in the Ambulatory Period by study arm.

**Table 53 Percent Change from Baseline in COHb in Whole Blood (%) by Study Arm During the Ambulatory Period (PP Set)**

Study Arm	Visit	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 5	76	-49.24	15.099	-78.4	-49.53	-4.8
	Day 30	74	-41.14	18.936	-72.2	-42.58	33.3
	Day 60	71	-39.19	21.030	-69.4	-44.90	47.6
	Day 90	70	-39.18	21.121	-71.9	-41.41	52.4
mCC	Day 5	42	8.90	18.963	-32.9	7.05	51.9
	Day 30	41	20.15	32.154	-32.0	12.96	117.9
	Day 60	41	17.68	32.349	-31.1	9.30	118.5
	Day 90	41	14.17	27.981	-31.3	10.13	89.7
SA	Day 5	39	-49.11	16.379	-70.4	-53.66	-8.8
	Day 30	39	-41.78	17.418	-71.1	-45.90	-6.3
	Day 60	38	-36.78	23.157	-67.1	-46.85	46.9
	Day 90	37	-36.34	20.951	-65.4	-41.67	14.7

Abbreviations: COHb = carboxyhemoglobin; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS 2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.1.1](#).

During the Ambulatory Period, the profile of the mean COHb in the THS 2.2 Menthol arm was comparable to that of the SA arm ([Figure 4](#)). Geometric mean COHb values in the THS 2.2 Menthol arm remained decreased from baseline (5.11%) on Days 30, 60, and 90, with values of 2.89%, 2.98%, and 2.97%, respectively. In contrast, in the mCC arm, COHb values were greater than baseline with values of 6.00%, 5.87%, and 5.73% for Days 30, 60, and 90, respectively. These values corresponded to percent changes from baseline on Day 90 of -39.18% and 14.17% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean COHb values during the Ambulatory Period remained decreased from baseline (5.15%), as expected, with a -36.34% change from baseline on Day 90 (3.04%).

Analysis of blood COHb (%) for THS 2.2 Menthol users versus mCC use and SA on Day 90 are tabulated in [Appendix 15, Table 15.2.3.2](#) and [Table 15.2.3.4](#) for the PP Set and in [Table 15.2.3.3](#) and [15.2.3.5](#) for the FAS. In addition, sensitivity analysis including analysis of the Compliant Population and use of a mixed model on the PP Set was performed, and these analyses are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 54](#).

**Table 54 Analysis of Blood COHb (%) versus mCC and SA on Day 90 (PP Set)**

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV (%)	95% CI
THS m2.2	70	2.96	51.72	18.97	48.07, 55.65
mCC	41	5.73			

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV (%)	95% CI
THS m2.2	70	2.96	97.10	18.97	90.03, 104.72
SA	37	3.05			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; COHb = carboxyhemoglobin; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. P-value is for the one-sided test for comparison between THS m2.2 and mCC.

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

On Day 90, the LS mean of COHb in subjects who switched to THS 2.2 Menthol use was 48.28% lower than that of subjects who continued to smoke mCC (95% CI: 44.35, 51.93; p-value <0.001).

On Day 90, the LS mean of COHb in subjects who switched to THS 2.2 Menthol use was comparable to that of subjects who abstained from smoking, with the 95% CIs spanning 100%.

An additional sensitivity analysis using a mixed model approach showed consistent results on Day 90 ([Appendix 15, Table 15.2.3.6](#)), with the LS mean of COHb in subjects who switched to THS 2.2 Menthol being 48.27% lower than that of subjects who continued to smoke mCC (95% CI: 44.32, 51.95; p-value <0.001).

In addition, during the Ambulatory Period, the Compliant Population was analyzed ([Appendix 15, Table 15.2.3.7](#)), which showed consistent results on Day 90 to the PP Set analysis, with the LS mean of COHb in subjects who switched to THS 2.2 Menthol being 48.69% lower than that of subjects who continued to smoke mCC (95% CI: 44.74, 52.37; p-value <0.001).



11.2.1.2 Monohydroxybutenyl Mercapturic Acid in 24-hour Urine During the Ambulatory Period

Subject listings and descriptive statistics of MHBMA data are provided as described in [Section 11.1.2](#). Geometric mean and 95% CIs for MHBMA throughout the study are presented graphically in [Appendix 15, Figure 15.1.1.2, Figure 15.1.1.3, and Figure 15.1.1.4](#) for the PP Set, Compliant Population, and the FAS, respectively. Data for the PP Set are also provided in [Figure 5](#).

[Table 55](#) presents the results of the MHBMA concentrations adjusted for creatinine at each time point in the Ambulatory Period by study arm.

Table 55 Absolute Values of MHBMA Urinary Concentrations Adjusted for Creatinine (pg/mg creat) by Study Arm During the Ambulatory Period (PP Set)

Study Arm	Visit	Number of	Geometric				
		Subjects	Mean	CV (%)	Min	Median	Max
THS m2.2	Baseline	76	653.78	115.03	80.8	708.14	4067.8
	Day 5	76	81.71	35.50	27.3	81.39	150.6
	Day 30	74	139.19	61.13	39.1	143.41	708.2
	Day 60	71	142.50	59.77	41.7	139.64	759.7
	Day 90	70	141.74	76.23	30.7	122.80	3645.2
mCC	Baseline	42	737.29	114.14	145.8	756.44	3506.2
	Day 5	42	622.58	132.98	109.2	607.12	3901.1
	Day 30	41	790.61	124.30	135.5	875.78	4058.8
	Day 60	41	799.06	109.15	182.8	820.51	3539.7
	Day 90	41	785.27	126.46	77.9	936.64	3942.3
SA	Baseline	39	614.87	122.18	139.2	562.84	2896.8
	Day 5	39	80.72	41.57	30.7	81.43	202.4
	Day 30	39	158.15	68.78	46.3	176.40	492.2
	Day 60	38	148.73	67.73	39.4	143.62	905.4
	Day 90	37	136.83	57.80	58.6	132.28	473.8

Abbreviations: CV = coefficient of variation; Max = maximum; mCC = Menthol conventional cigarette; MHBMA = Monohydroxybutenyl mercapturic acid; Min = minimum; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS 2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.2.1](#).

[Table 56](#) presents overall percentage change from baseline in MHBMA concentration adjusted for creatinine in the Ambulatory Period by study arm.



Table 56 Percent Change from Baseline MHBMA Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm During the Ambulatory Period (PP Set)

Study Arm	Visit	Number of Arithmetic		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 5	76	-80.54	20.866	-98.3	-86.85	37.3
	Day 30	74	-67.93	30.046	-96.9	-80.99	37.5
	Day 60	71	-69.13	27.675	-95.9	-83.13	29.7
	Day 90	70	-64.30	41.414	-96.9	-79.24	179.1
mCC	Day 5	42	-11.98	28.782	-53.6	-17.42	113.6
	Day 30	41	13.72	46.766	-68.2	8.43	151.5
	Day 60	41	15.09	49.173	-74.4	3.54	171.5
	Day 90	41	15.68	63.221	-53.0	-1.47	278.8
SA	Day 5	39	-78.67	18.978	-98.1	-86.78	-35.9
	Day 30	39	-60.26	35.775	-97.9	-70.87	28.5
	Day 60	38	-60.09	40.969	-95.9	-72.82	61.1
	Day 90	37	-66.12	29.207	-96.8	-74.59	21.2

Abbreviations: Max = maximum; mCC = conventional cigarette; MHBMA = Monohydroxybutenyl mercapturic acid; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Data Source: [Appendix 15, Table 15.2.4.2.1](#).

During the Ambulatory Period, the profile of the mean MHBMA urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was comparable to that of the SA arm. Geometric mean MHBMA values in the THS 2.2 Menthol arm remained decreased from baseline (653.78 pg/mg creat) on Days 30, 60, and 90 with values of 139.19, 142.50, and 141.74 pg/mg creat, respectively. In contrast, in the mCC arm, MHBMA values were greater than baseline, with 790.61, 799.06, and 785.27% for Days 30, 60, and 90, respectively. These values corresponded to percent changes from baseline on Day 90 of -64.30% and 15.68% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean MHBMA values during the Ambulatory Period remained decreased from baseline (614.87 pg/mg creat), as expected, with a -66.12% change from baseline on Day 90 (136.83 pg/mg creat).

Analysis of MHBMA urinary concentrations adjusted for creatinine and urinary quantity of MHBMA excreted over 24 hours for THS 2.2 Menthol users versus mCC use, and versus SA on Day 90 are tabulated in [Appendix 15, 15.2.3.2](#) and [Table 15.2.3.4](#) for the PP Set and in [Table 15.2.3.3](#) and [15.2.3.5](#) for the FAS. In addition, sensitivity analysis including analysis of the Compliant Population and use of a mixed model on the PP Set was performed, and these analyses are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set is also provided in [Table 57](#).

**Table 57 Analysis of MHBMA versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2: mCC) (%)		
				CV%	95% CI	
Quantity excreted over 24 hours (ng)	THS m2.2	70	158.79	19.95	72.76	15.46, 25.73
	mCC	41	796.02			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	143.17	19.01	74.05	14.68, 24.61
	mCC	41	753.25			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)		
				CV%	95% CI	
Quantity excreted over 24 hours (ng)	THS m2.2	70	158.79	102.01	72.76	78.49, 132.56
	SA	37	155.67			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	143.17	101.34	74.05	77.68, 132.20
	SA	37	141.28			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; MHBMA = Monohydroxybutenyl mercapturic acid; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of MHBMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 80.99% lower than that of subjects who continued to smoke mCC (95% CI: 75.39, 85.32; p-value <0.001). The results for the quantity of MHBMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of MHBMA urinary concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs of both assessments spanning 100%.

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.6](#)), with the LS mean of MHBMA urinary



concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use being 80.99% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 75.34, 85.34; p-value <0.001).

In addition, during the Ambulatory Period the Compliant Population was analyzed on Day 90 ([Appendix 15, Table 15.2.3.7](#)), which showed consistent results to the PP Set analysis, with the LS mean of MHBMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol being 81.69% lower than that of subjects who continued to smoke mCC (95% CI: 76.18, 85.92; p-value <0.001).

11.2.1.3 3-Hydroxypropylmercapturic Acid in 24-hour Urine During the Ambulatory Period

Subject listings and descriptive statistics of 3-HPMA are provided as described in [Section 11.1.3](#). Geometric mean and 95% CIs for 3-HPMA throughout the study are presented graphically in [Appendix 15, Figure 15.1.1.2, Figure 15.1.1.3, and Figure 15.1.1.4](#) for the PP Set, Compliant Population, and FAS, respectively. Data for the PP Set are presented in [Figure 6](#).

[Table 58](#) presents the results of the 3-HPMA concentrations adjusted for creatinine at each time point in the Ambulatory Period by study arm.

**Table 58 Absolute Values of 3-HPMA Urinary Concentrations Adjusted for Creatinine (ng/mg creat) by Study Arm During the Ambulatory Period (PP Set)**

Study Arm	Visit	Number of Subjects	Geometric Mean	CV (%)	Min	Median	Max
THS m2.2	Baseline	76	667.53	49.95	264.9	681.14	2669.4
	Day 5	76	304.68	30.46	163.3	300.59	631.0
	Day 30	74	330.44	32.51	162.5	331.06	676.2
	Day 60	71	334.96	34.76	164.6	322.93	970.0
	Day 90	70	386.37	34.98	225.1	392.90	945.4
mCC	Baseline	42	642.20	51.11	253.0	617.49	2075.8
	Day 5	42	591.33	51.99	261.3	587.31	1548.8
	Day 30	41	659.07	45.57	300.9	664.95	1637.1
	Day 60	41	684.81	51.65	215.1	648.99	1795.3
	Day 90	41	695.58	48.02	271.5	392.90	1945.2
SA	Baseline	39	691.14	53.57	273.3	660.55	1873.9
	Day 5	39	186.71	42.96	48.9	195.57	366.7
	Day 30	39	271.96	45.07	105.8	278.06	812.1
	Day 60	38	255.75	42.47	94.7	257.79	689.9
	Day 90	37	276.13	41.02	121.9	267.33	678.1

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CV = coefficient of variation; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS 2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.3.1](#).

[Table 59](#) presents overall percentage change from baseline in 3-HPMA concentration adjusted for creatinine in the Ambulatory Period by study arm.

**Table 59** Percent Change from Baseline 3-HPMA Concentration Adjusted for Creatinine (ng/mg creat) by Study Arm During the Ambulatory Period (PP Set)

Study Arm	Visit	Number of Arithmetic		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 5	76	-50.90	19.081	-80.1	-54.84	15.5
	Day 30	74	-46.34	24.601	-86.3	-51.02	40.9
	Day 60	71	-46.39	25.240	-81.6	-53.98	32.8
	Day 90	70	-37.09	32.660	-76.5	-45.15	108.3
mCC	Day 5	42	-5.48	21.382	-47.2	-5.10	48.3
	Day 30	41	11.91	42.610	-68.8	5.87	159.9
	Day 60	41	16.05	42.736	-57.4	8.49	122.4
	Day 90	41	18.63	48.990	-50.4	12.10	169.2
SA	Day 5	39	-68.42	18.422	-92.1	-71.37	1.0
	Day 30	39	-52.26	31.645	-87.5	-64.96	34.0
	Day 60	38	-55.85	25.284	-88.8	-59.12	13.6
	Day 90	37	-48.38	41.475	-88.4	-58.99	148.1

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; Max = maximum; mCC = conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.3.1](#).

During the Ambulatory Period, the profile of the mean 3-HPMA urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was comparable to that of the SA arm. Geometric mean 3-HPMA values in the THS 2.2 Menthol arm remained decreased from baseline (667.53 ng/mg creat) on Days 30, 60, and 90, with values of 330.44, 334.96, and 386.37 ng/mg creat, respectively. In contrast, in the mCC arm, 3-HPMA values were greater than baseline, with values of 659.07, 684.81, 695.58 ng/mg creat on Days 30, 60, and 90, respectively. These values corresponded to percent changes from baseline on Day 90 of -37.09% and 18.63% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean 3-HPMA values during the Ambulatory Period remained decreased from baseline (691.14 ng/mg creat), as expected, with -48.38% change from baseline on Day 90 (276.13 ng/mg creat).

Analysis of 3-HPMA urinary concentrations adjusted for creatinine and urinary quantity of 3-HPMA excreted over 24 hours for THS 2.2 Menthol users versus mCC use, and versus SA on Day 90 are tabulated in [Appendix 15, Table 15.2.3.2](#) and [Table 15.2.3.4](#) for the PP Set and in [Table 15.2.3.3](#) and [15.2.3.5](#) for the FAS. In addition, sensitivity analysis including analysis of the Compliant Population and use of a mixed model on the PP Set was performed, and these analyses are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set is also provided in [Table 60](#).

**Table 60 Analysis of 3-HPMA versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	70	425.55	56.21	41.64	48.08, 65.70
	mCC	41	757.13			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	70	385.25	54.08	37.55	46.94, 62.32
	mCC	41	712.32			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	70	425.55	139.24	41.64	118.57, 163.52
	SA	37	305.62			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	70	385.25	138.52	37.55	119.70, 160.30
	SA	37	278.13			

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; ANCOVA = analysis of covariance; mCC = menthol conventional cigarette; CI = confidence interval; CV = coefficient of variance; LS = least squares; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of 3-HPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 45.92% lower than that of subjects who continued to smoke mCC (95% CI: 37.68, 53.06; p-value <0.001). The results for the quantity of 3-HPMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, LS means of 3-HPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 38.52% higher compared to that of subjects who abstained from smoking (95% CI: 119.70, 160.30).

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.6](#)), with the LS mean of 3-HPMA urinary



concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol being 46.10% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 37.84, 53.26; p-value <0.001).

In addition, during the Ambulatory Period, the Compliant Population was analyzed on Day 90 ([Appendix 15, Table 15.2.3.7](#)), which showed consistent results to the PP Set analysis, with the LS mean of 3-HPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol being 45.67% lower than that of subjects who continued to smoke mCC (95% CI: 37.21, 52.98; p-value <0.001).

11.2.1.4 S-phenylmercapturic Acid in 24-hour Urine During the Ambulatory Period

Subject listings and descriptive statistics of S-PMA concentration adjusted for creatinine data during the course of the study are provided as described in [Section 11.1.4](#). Geometric mean and 95% CIs for S-PMA throughout the study are presented graphically in [Appendix 15, Figure 15.1.1.2, Figure 15.1.1.3, and Figure 15.1.1.4](#) for the PP Set, Compliant Population, and FAS, respectively. Data for the PP Set are presented in [Figure 7](#).

[Table 61](#) presents the results of the S-PMA concentrations adjusted for creatinine at each time point in the Ambulatory Period by study arm.

**Table 61 Absolute Values of S-PMA Urinary Concentrations Adjusted for Creatinine (pg/mg creat) by Study Arm During the Ambulatory Period (PP Set)**

Study Arm	Visit	Number of Subjects	Geometric Mean	CV (%)	Min	Median	Max
THS m2.2	Baseline	76	1058.84	115.52	167.6	1274.20	6057.5
	Day 5	76	118.36	44.66	51.5	119.32	280.7
	Day 30	74	115.39	70.47	20.2	117.73	1013.6
	Day 60	71	115.00	88.10	16.8	110.36	1489.3
	Day 90	70	145.58	87.23	19.8	128.33	1165.8
mCC	Baseline	42	1096.79	115.64	206.8	1041.05	6078.8
	Day 5	42	1096.47	129.25	174.4	1103.64	7234.4
	Day 30	41	1067.05	132.92	162.7	1157.78	6287.7
	Day 60	41	995.50	115.48	200.0	910.26	7724.9
	Day 90	41	1157.25	127.57	168.7	1102.30	8096.2
SA	Baseline	39	1027.37	123.71	190.4	902.99	5315.9
	Day 5	39	102.51	62.05	21.4	106.75	279.9
	Day 30	39	97.51	76.46	29.2	94.44	516.7
	Day 60	38	111.24	93.93	23.6	106.36	1223.0
	Day 90	37	144.07	96.75	19.3	146.89	1378.4

Abbreviations: CV = coefficient of variation; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS 2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15](#), [Table 15.2.4.4.1](#).

[Table 62](#) presents overall percentage change from baseline in S-PMA concentration adjusted for creatinine in the Ambulatory Period by study arm.



Table 62 Percent Change from Baseline S-PMA Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm During the Ambulatory Period (PP Set)

Study Arm	Visit	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 5	76	-85.88	10.628	-97.5	-89.85	-41.6
	Day 30	74	-84.93	13.698	-98.4	-89.98	-23.5
	Day 60	71	-85.50	13.211	-98.4	-90.34	-36.5
	Day 90	70	-81.21	15.516	-97.5	-88.05	-25.7
mCC	Day 5	42	5.44	35.808	-47.8	1.42	100.9
	Day 30	41	6.60	53.718	-63.6	-2.80	176.7
	Day 60	41	-1.25	44.903	-78.3	-4.65	113.3
	Day 90	41	14.28	57.385	-54.5	2.76	190.3
SA	Day 5	39	-86.80	10.811	-98.1	-90.78	-45.0
	Day 30	39	-87.52	8.667	-98.7	-88.62	-66.8
	Day 60	38	-82.67	20.597	-98.1	-89.75	-6.7
	Day 90	37	-75.57	29.054	-98.6	-88.03	52.7

Abbreviations: Max = maximum; mCC = conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.4.1](#).

During the Ambulatory Period, the profile of the mean S-PMA urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was comparable to that of the SA arm. Geometric mean S-PMA values in the THS 2.2 Menthol arm remained decreased from baseline (1058.84 pg/mg creat) on Days 30, 60, and 90 with values of 115.39, 115.00, and 145.58 pg/mg creat, respectively. In contrast, in the mCC arm, S-PMA values at baseline (1096.79 pg/mg creat) were 1067.05, 995.50, and 1157.25 pg/mg creat, on Days 30, 60, and 90, respectively. These values corresponded to percent changes from baseline on Day 90 of -81.21% and 14.28% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean S-PMA values during the Ambulatory Period remained decreased from baseline (1027.37 pg/mg creat), as expected, with a -75.57% change from baseline on Day 90 (144.07 pg/mg creat).

Analysis of S-PMA urinary concentrations adjusted for creatinine and urinary quantity of S-PMA excreted over 24 hours for THS 2.2 Menthol users versus mCC use, and versus SA on Day 90 are tabulated in [Appendix 15, Table 15.2.3.2](#) and [Table 15.2.3.4](#) for the PP Set and in [Table 15.2.3.3](#) and [15.2.3.5](#) for the FAS. In addition, sensitivity analysis including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and these analyses are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set is also provided in [Table 63](#).

**Table 63 Analysis of S-PMA versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	165.62	13.40	71.82	10.42, 17.23
	mCC	41	1236.20			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	148.85	12.80	74.27	9.88, 16.58
	mCC	41	1162.70			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	165.62	99.73	71.82	76.95, 129.24
	SA	37	166.08			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	148.85	98.78	74.27	75.68, 128.94
	SA	37	150.69			

Abbreviations: ANCOVA = analysis of covariance; mCC = menthol conventional cigarette; CI = confidence interval; CV = coefficient of variance; LS = least squares; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of S-PMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 87.20% lower than that of subjects who continued to smoke mCC (95% CI: 83.42, 90.12; p-value <0.001). The results for the quantity of S-PMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of S-PMA urinary concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.



An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.6](#)), with the LS mean of S-PMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use being 87.01% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 89.96, 83.18; p-value <0.001).

In addition, during the Ambulatory Period, the Compliant Population was analyzed ([Appendix 15, Table 15.2.3.7](#)), which showed consistent results to the PP Set analysis, with the LS mean of S-PMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol being 87.78% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 84.18, 90.56; p-value <0.001).

11.2.1.5 Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in 24-hour Urine During the Confinement Period

Subject listings and descriptive statistics of Total NNAL are provided as described in [Section 11.1.5](#). Geometric mean and 95% CIs for Total NNAL throughout the study are presented graphically in [Appendix 15, Figure 15.1.1.2](#), [Figure 15.1.1.3](#), and [Figure 15.1.1.4](#) for the PP Set, Compliant Population, and FAS, respectively. Data for the PP Set are presented in [Figure 8](#).

The profile of the mean Total NNAL urinary concentrations adjusted for creatinine in the THS 2.2 Menthol arm was comparable to that of the SA arm, with a gradual decrease from Day 1 to Day 5. Geometric mean Total NNAL values decreased in the THS 2.2 Menthol arm from baseline (85.64 pg/mg creat) to Day 5 (37.90 pg/mg creat) in contrast to Total NNAL in the mCC arm, with a baseline value of 84.77 pg/mg creat) and a Day 5 value of 85.94 pg/mg creat. These values corresponded to percent changes from baseline of -54.39% and 3.91% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total NNAL values decreased from baseline (79.54 pg/mg creat) to Day 5 (29.58 pg/mg creat), as expected, which corresponded to a -61.03% change from baseline.

There was no apparent differences in mean levels of Total NNAL between male and female subjects at baseline, but at Day 5, there were mean decreases from baseline in Total NNAL in the SA arm of -55.50% for male subjects compared to -68.17% in female subjects (95% CIs: -58.66, -52.34; -73.40, -62.95, respectively).

Analyses of Total NNAL urinary concentration adjusted for creatinine and urinary quantity of Total NNAL excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 64](#).

**Table 64 Analysis of Total NNAL versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	42.93	40.76	31.11	36.31, 45.76		
	mCC	42	105.32					
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	36.95	43.69	26.09	39.62, 48.17		
	mCC	42	84.57					

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	42.93	114.76	31.11	101.94, 129.19		
	SA	39	37.40					
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	36.95	119.61	26.09	108.23, 132.19		
	SA	39	30.89					

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of Total NNAL concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 56.31% lower than that of subjects who continued to smoke mCC (95% CI: 51.83, 60.38; p-value <0.001). The results for the quantity of Total NNAL excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS mean of Total NNAL concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 19.61% higher than that of subjects who abstained from smoking, with the lower bound of the 95% CI greater than 100% (95% CI: 108.23, 132.19). However, most of the reduction observed in the SA arm compared to the mCC arm, was also observed in the THS 2.2 Menthol arm. The results for the quantity of Total NNAL excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.



Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

11.2.2 Analysis of COHb, MHBMA, 3-HPMA, S-PMA on Day 5 and Total NNAL on Day 90 versus Smoking Abstinence

Analyses of evening COHb and urinary concentrations of MHBMA, 3-HPMA, S-PMA, and Total NNAL adjusted for creatinine for THS 2.2 Menthol use versus SA on Day 5 and Day 90 are tabulated in [Appendix 15, Table 15.2.3.2](#) and [Table 15.2.3.3](#) for the PP Set and FAS, respectively. Analyses of urinary concentrations excreted over 24 hours are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. Data for the PP Set is also provided in [Table 65](#).



Table 65 Analysis of COHb, MHBMA, 3-HPMA, S-PMA on Day 5 and Total NNAL on Day 90 versus SA (PP Set)

Biomarker/ Time point	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV (%)	95% CI
				(THS m2.2:SA) (%)		
Evening COHb (%)						
Day 5	THS m2.2	76	2.47	99.31	17.24	92.91, 106.15
	SA	39	2.49			
Urinary MHBMA (pg/mg creat)						
Day 5	THS m2.2	76	83.21	99.57	58.68	80.56, 123.06
	SA	39	83.57			
Urinary MHBMA (ng)						
Day 5	THS m2.2	76	95.28	95.39	62.25	76.33, 119.20
	SA	39	99.88			
Urinary 3-HPMA (ng/mg creat)						
Day 5	THS m2.2	76	304.56	165.87	32.72	146.50, 187.81
	SA	39	183.61			
Urinary 3-HPMA (µg)						
Day 5	THS m2.2	76	350.10	158.31	36.50	137.94, 181.68
	SA	39	221.15			
Urinary S-PMA (pg/mg creat)						
Day 5	THS m2.2	76	119.18	113.70	46.63	95.67, 135.12
	SA	39	104.83			
Urinary S-PMA (ng)						
Day 5	THS m2.2	76	137.25	108.85	52.48	89.83, 131.89
	SA	39	126.09			
Total NNAL (pg/mg creat)						
Day 90	THS m2.2	70	22.48	150.85	86.42	111.62, 203.87
	SA	37	14.90			
Total NNAL (ng)						
Day 90	THS m2.2	70	25.09	152.53	87.89	112.44, 206.91
	SA	37	16.45			

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; ANCOVA = analysis of covariance; CI = confidence interval; COHb = carboxyhemoglobin; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares. Data Source: [Appendix 15, Table 15.2.3.2](#) and [15.2.3.4](#).



There were no notable differences observed between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking for evening COHb and urinary concentrations of MHBMA, and S-PMA adjusted for creatinine on Day 5 in the Confinement Period, with the 95% CIs for these parameters spanning 100%.

For urinary 3-HPMA adjusted for creatinine on Day 5, the LS means in subjects who switched to THS 2.2 Menthol use was approximately 66% higher than that of subjects who abstained from smoking, with the lower limit of the 95% CI being greater than 100% (95% CI: 146.50, 187.81). The results for the quantity of S-PMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

For Total NNAL adjusted for creatinine on Day 90, the LS means in subjects who switched to THS 2.2 Menthol use was approximately 51% higher compared to SA on Day 90, but most of the reduction observed in the SA arm compared to the mCC arm was also observed in the THS 2.2 Menthol arm ([Figure 8](#)). The results for the quantity of Total NNAL excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

11.2.3 Analysis of Other Biomarkers of Exposure During Study

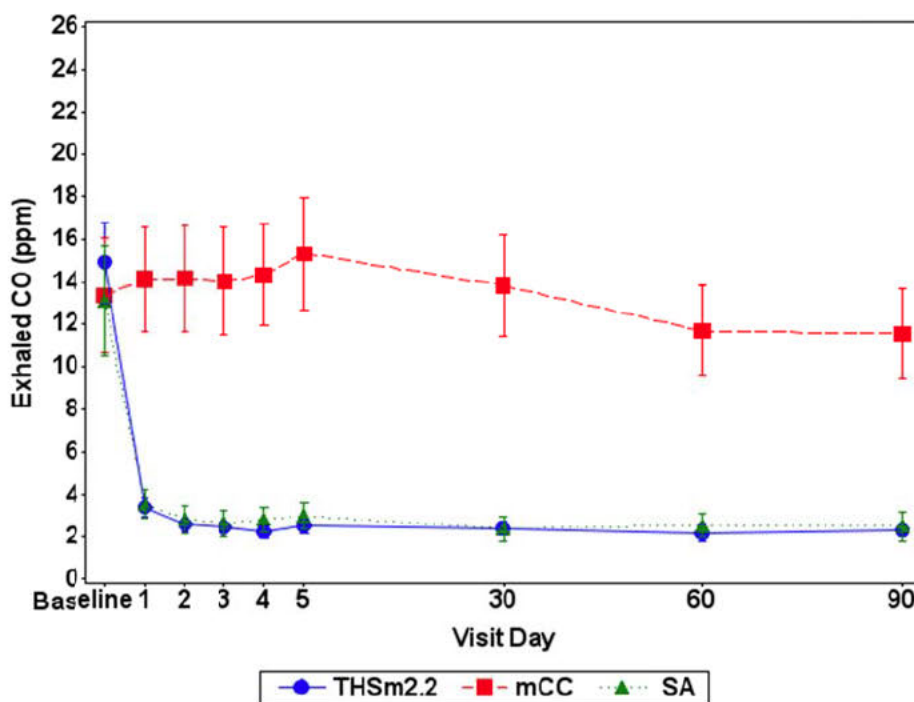
11.2.3.1 Exhaled Carbon Monoxide During the Study

Subject listings of exhaled CO data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of exhaled CO assessment data during the course of the study together with changes from baseline are provided in [Appendix 15, Table 15.2.4.6.1](#) and [Table 15.2.4.6.2](#) for the PP Set and FAS, respectively. Arithmetic mean and 95% CIs for exhaled CO are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 9](#).



Figure 9 Arithmetic Mean and 95% CI for Exhaled CO (ppm) During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; CO = carbon monoxide; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#)

The profile of mean exhaled CO in the THS 2.2 Menthol arm was comparable to that of the SA arm, with the majority of the decrease in exhaled CO being achieved by Day 1, before plateauing thereafter. Arithmetic mean exhaled CO values decreased in the THS 2.2 Menthol arm from the evening of Day 0 (14.89 ppm) to the evening of Day 5 (2.31 ppm), in contrast to exhaled CO in the mCC arm, which remained similar from the evening on Day 0 (13.36 ppm) to the evening of Day 5 (15.10 ppm). These values corresponded to percent time-matched changes from baseline of -74.76% and 43.75% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, arithmetic mean exhaled CO values decreased from Day 0 (13.10 ppm) to Day 5 (3.00 ppm), as expected, which corresponded to a -66.44% change from baseline.

During the Ambulatory Period, arithmetic mean exhaled CO values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (2.41, 2.17, and 2.31 ppm, respectively), whereas exhaled CO in the mCC arm was 13.83, 11.71, and



11.56 ppm on Days 30, 60, and 90, respectively. These values corresponded to percent changes from baseline on Day 90 of -72.63% and 24.54% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, arithmetic mean exhaled CO values remained decreased from baseline, as expected, with a -74.46% change from baseline on Day 90 (2.51 ppm).

Analyses of exhaled CO for THS 2.2 Menthol use versus mCC use and versus SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are tabulated in [Table 66](#) and [Table 67](#) for the Day 5 and Day 90, respectively.

Table 66 Analysis of Exhaled CO (ppm) versus mCC and SA on Day 5 (PP Set)

Exposure	Number of Subjects	Geometric LS Mean	THS m2.2 - mCC difference (ppm)	95% CI
THS m2.2	76	2.29	-13.10	-14.70, -11.50
mCC	42	15.39		

Exposure	Number of Subjects	Geometric LS Mean	THS m2.2 – SA difference (ppm)	95% CI
THS m2.2	76	2.29	-0.85	-2.49, 0.79
SA	39	3.14		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CO = carbon monoxide;

LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence;

THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the difference in LS means of exhaled CO in subjects who switched to THS 2.2 Menthol use compared to that of subjects who continued to smoke mCC was -13.10 ppm (95% CI: -14.70, -11.50; p-value <0.001).

On Day 5, no notable difference in LS means of exhaled CO in subjects who switched to THS 2.2 Menthol use compared to that of subjects who abstained from smoking was observed, with the 95% CI spanning 0.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

**Table 67 Analysis of Exhaled CO (ppm) versus mCC and SA on Day 90 (PP Set)**

Exposure	Number of Subjects	Geometric LS Mean	THS m2.2 - mCC difference (ppm)	95% CI
THS m2.2	70	2.36	-9.28	-10.75, -7.81
mCC	41	11.65		

Exposure	Number of Subjects	Geometric LS Mean	THS m2.2 – SA difference (ppm)	95% CI
THS m2.2	70	2.36	-0.23	-1.75, 1.29
SA	37	2.59		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CO = carbon monoxide; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the difference in LS means of exhaled CO in subjects who switched to THS 2.2 Menthol use compared to that of subjects who continued to smoke mCC was -9.28 (95% CI: -10.75, -7.81; p-value <0.001).

On Day 90, the difference in LS means of exhaled CO in subjects who switched to THS 2.2 Menthol use was comparable to that of subjects who abstained from smoking, with 95% CI of the difference in LS means spanning 0.

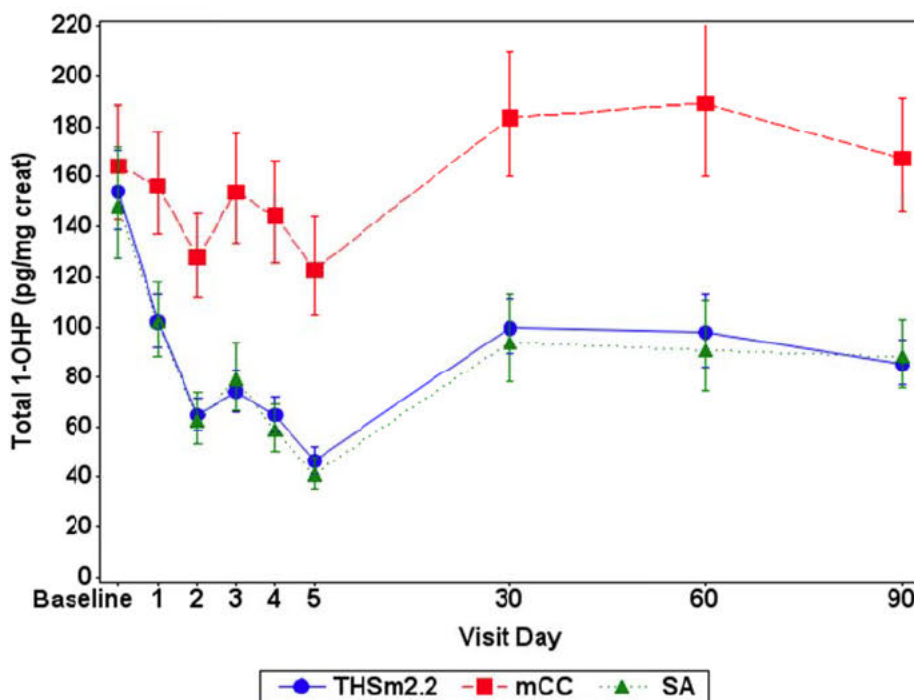
Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population, showed consistent results to those presented.

11.2.3.2 Total 1-hydroxypyrene in 24-hour Urine During the Study

Subject listings of Total 1-OHP data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of Total 1-OHP concentration adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.7.1](#) and [Table 15.2.4.7.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for Total 1-OHP urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 10](#).

Figure 10 Geometric Mean and 95% CI Total 1-OHP Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 1-OHP = 1-hydroxypyrene; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean 1-OHP in the THS 2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Days 1 and 2, followed by a further decrease observed on Days 4 and 5. Geometric mean Total 1-OHP values decreased in the THS 2.2 Menthol arm from baseline (153.98 pg/mg creat) to Day 5 (46.35 pg/mg creat) whereas Total 1-OHP in the mCC arm had a baseline value of 164.33 pg/mg creat and a Day 5 value of 122.90 pg/mg creat. These values corresponded to percent changes from baseline on Day 5 of -68.08% and -25.00% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total 1-OHP values decreased from baseline (148.01 pg/mg creat) to Day 5 (46.14 pg/mg creat), as expected, corresponding to a -68.84% change from baseline.

During the Ambulatory Period, geometric mean Total 1-OHP values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (99.69, 97.95, and



85.47 pg/mg creat, respectively), but were higher than the Day 5 value. Total 1-OHP in the mCC arm was greater than baseline on Days 30, 60, and 90 (183.50, 189.23, and 167.38 pg/mg creat, respectively). These values corresponded to percent changes from baseline on Day 90 of -36.75% and 7.87% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total 1-OHP values remained decreased from baseline, as expected, with a -31.39% change from baseline on Day 90 (88.21 pg/mg creat).

Analyses of Total 1-OHP urinary concentration adjusted for creatinine and urinary quantity of Total 1-OHP excreted over 24 hours for THS 2.2 Menthol use versus mCC use, and versus SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 68](#) and [Table 69](#).

**Table 68 Analysis of Total 1-OHP versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2: mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	54.63	36.36	40.91	31.30, 42.24
	mCC	42	150.23			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	47.34	39.18	31.60	34.82, 44.07
	mCC	42	120.83			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	54.63	105.65	40.91	90.64, 123.15
	SA	39	51.71			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	47.34	109.65	31.60	97.23, 123.66
	SA	39	43.17			

Abbreviations: 1-OHP = 1-hydroxypyrene; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of Total 1-OHP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 60.82% lower than that of subjects who continued to smoke mCC (95% CI: 55.93, 65.18; p-value <0.001). The results for the quantity of Total 1-OHP excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both Total 1-OHP concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 69 Analysis of Total 1-OHP versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	96.19	53.97	46.16	45.46, 64.06
	mCC	41	178.23			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	86.81	52.02	39.54	44.83, 60.38
	mCC	41	166.86			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	96.19	95.72	46.16	80.22, 114.22
	SA	37	100.49			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	86.81	94.78	39.54	81.31, 110.48
	SA	37	91.59			

Abbreviations: 1-OHP = 1-hydroxypyrene; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of Total 1-OHP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 47.98% lower than that of subjects who continued to smoke mCC (95% CI: 39.62, 55.17; p-value <0.001). The results for the quantity of Total 1-OHP excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both Total 1-OHP concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

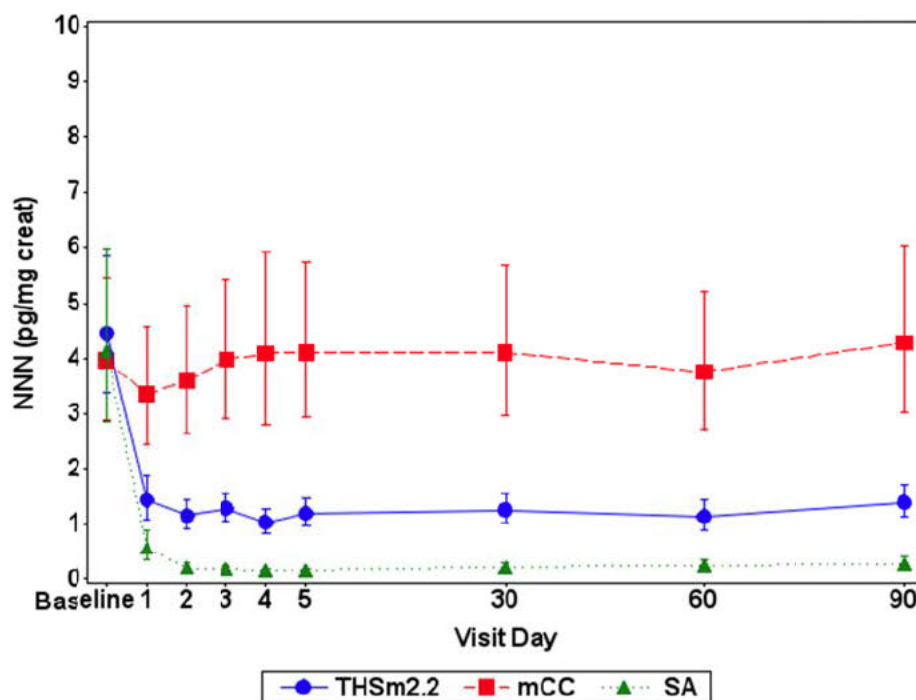
11.2.3.3 Total N-nitrosornicotine in 24-hour Urine During the Study

Subject listings of Total NNN data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of Total NNN adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.8.1](#) and [Table 15.2.4.8.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for Total NNN urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 11](#).



Figure 11 Geometric Mean and 95% CI Total NNN Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol; NNN = N-nitrosornicotine. Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean Total NNN in the THSm2.2 Menthol arm was similar to that of the SA arm, with the majority of the decrease from baseline being achieved by Day 1, before plateauing thereafter. Geometric mean Total NNN values decreased in the THSm2.2 Menthol arm from baseline (4.45 pg/mg creat) to Day 5 (1.20 pg/mg creat) whereas Total NNN in the mCC arm had a baseline value of 3.97 pg/mg creat and a Day 5 value of 4.10 pg/mg creat. These values corresponded to percent changes from baseline on Day 5 of -65.80% and 20.30% for the THSm2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total NNN values decreased from baseline (4.13 pg/mg creat) to Day 5 (0.15 pg/mg creat), as expected, corresponding to a -93.89% change from baseline.

During the Ambulatory period, geometric mean Total NNN values remained decreased from baseline in the THSm2.2 Menthol arm on Days 30, 60, and 90 (1.26, 1.14, and 1.40 pg/mg creat, respectively), whereas Total NNN in the mCC arm on Days 30, 60, and 90 was 4.10, 3.76, and 4.28 pg/mg creat, respectively. These values corresponded to



percent changes from baseline on Day 90 of -54.33% and 34.37% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total NNN values remained decreased from baseline, as expected, with a -86.48% change from baseline on Day 90 (0.26 pg/mg creat).

Analyses of Total NNN urinary concentration adjusted for creatinine and urinary quantity of Total NNN excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 70](#) and [Table 71](#).

**Table 70 Analysis of Total NNN versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	1.36	25.42	65.12	20.27, 31.89
	mCC	42	5.37			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1.18	27.02	61.48	21.75, 33.55
	mCC	42	4.38			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	1.36	752.55	65.12	597.03, 948.57
	SA	39	0.18			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1.18	786.46	61.84	630.18, 981.50
	SA	39	0.15			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; NNN = N-nitrosornicotine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of Total NNN concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 72.98% lower than that of subjects who continued to smoke mCC (95% CI: 66.45, 78.25; p-value <0.001). The results for the quantity of Total NNN excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS mean of Total NNN concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 7.87-fold higher than that of subjects who abstained from smoking (95% CI: 630.18, 981.50). The results for the quantity of Total NNN excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.



Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 71 Analysis of Total NNN versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	1.51	30.43	89.91	22.53, 41.09
	mCC	41	4.96			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	1.36	29.31	94.14	21.48, 39.98
	mCC	41	4.62			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	1.51	494.06	89.91	362.51, 673.35
	SA	37	0.31			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	1.36	488.54	94.14	354.58, 673.12
	SA	37	0.28			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; NNN = N-nitrosornicotine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4.](#)

On Day 90, the LS mean of Total NNN concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 70.69% lower than that of subjects who continued to smoke mCC (95% CI: 60.02, 78.52; p-value <0.001). The results for the quantity of Total NNN excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.



On Day 90, the LS means of both Total NNN concentration adjusted for creatinine and quantity excreted over 24 hours were 4.89-fold and 4.94-fold higher in subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking, respectively (95% CIs: 354.58, 673.12 and 362.51, 673.35, respectively).

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population, showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

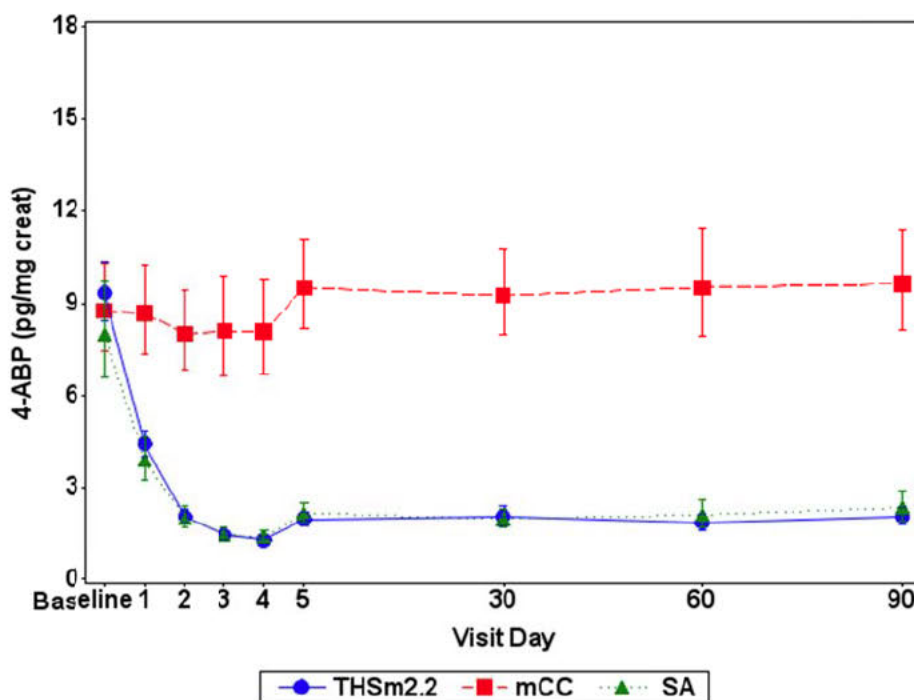
11.2.3.4 4-aminobiphenyl in 24-hour Urine During the Study

Subject listings of 4-ABP data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of 4-ABP adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.9.1](#) and [Table 15.2.4.9.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for 4-ABP urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 12](#).



Figure 12 Geometric Mean and 95% CI 4-ABP Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 4-ABP = 4-aminobiphenyl; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.1.2](#).

The profile of mean 4-ABP in the THS 2.2 Menthol arm was comparable to that of the SA arm, with maximum reduction in 4-ABP achieved by Day 4. Geometric mean 4-ABP values decreased in the THS 2.2 Menthol arm from baseline (9.33 pg/mg creat) to Day 5 (1.7 pg/mg creat), whereas 4-ABP in the mCC arm had a baseline value of 8.75 pg/mg creat and a Day 5 value of 9.50 pg/mg creat. These values corresponded to percent changes from baseline of -74.36% and 10.87% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 4-ABP values decreased from baseline (7.99 pg/mg creat) to Day 5 (2.16 pg/mg creat), as expected, which corresponded to a -4.19% change from baseline.

During the Ambulatory period, geometric mean 4-ABP values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (2.06, 1.85, and 2.07 pg/mg creat, respectively), whereas 4-ABP in the mCC arm was greater than baseline on Days 30, 60, and 90 (9.25, 9.51, and 9.62 pg/mg creat, respectively). These



values corresponded to percent changes from baseline on Day 90 of -72.57% and 24.84% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 4-ABP values remained decreased from baseline, as expected, with a -50.96% change from baseline on Day 90 (2.35 pg/mg creat).

Analyses of 4-ABP urinary concentration adjusted for creatinine and urinary quantity of 4-ABP excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated [Table 72](#) and [Table 73](#).

**Table 72 Analysis of 4-ABP versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	2.26	19.05	48.26	16.00, 22.69
	mCC	42	11.84			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1.96	20.10	44.68	17.08, 23.64
	mCC	42	9.76			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	2.26	82.92	48.26	69.28, 99.24
	SA	39	2.72			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1.96	86.22	44.68	72.93, 101.94
	SA	39	2.28			

Abbreviations: 4-ABP = 4-aminobiphenyl; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of 4-ABP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 79.90% lower than that of subjects who continued to smoke mCC (95% CI: 76.36, 82.92; p-value <0.001). The results for the quantity of 4-ABP excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of 4-ABP concentration adjusted for creatinine were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100%. The LS mean of 4-ABP quantity excreted over 24 hours was 17.08% lower in the THS 2.2 Menthol arm compared to subjects who abstained from smoking, with 95% CI of 0.76, 30.72; however, most of the reduction observed in the THS 2.2 arm compared to the mCC arm was also observed in the SA arm.



Analysis on the PP Set using a mixed model showed consistent results to those presented above. Analysis on the FAS showed that both 4-ABP concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100%.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 73 Analysis of 4-ABP versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	2.28	21.91	61.96	17.54, 27.36
	mCC	41	10.42			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	2.08	21.00	57.87	17.02, 25.89
	mCC	41	9.90			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	2.28	85.16	61.96	67.64, 107.22
	SA	37	2.68			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	2.08	85.76	57.87	69.00, 106.60
	SA	37	2.42			

Abbreviations: 4-ABP = 4-aminobiphenyl; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of 4-ABP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 79.0% lower than that of subjects who continued to smoke mCC (95% CI: 74.11, 82.98; p-value <0.001). The results for the quantity of



4-ABP excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both 4-ABP concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

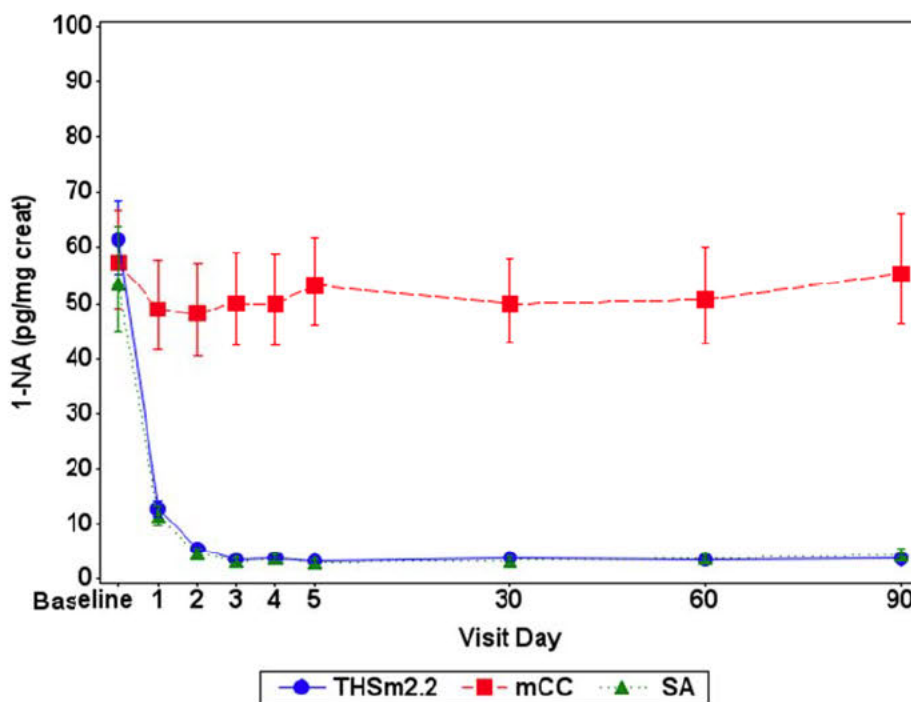
11.2.3.5 1-aminonaphthalene in 24-hour Urine During the Study

Subject listings of 1-NA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of 1-NA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.10.1](#) and [Table 15.2.4.10.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for 1-NA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 13](#).



Figure 13 Geometric Mean and 95% CI 1-NA Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 1-NA = 1-aminonaphthalene; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean 1-NA in the THS 2.2 Menthol arm was comparable to that of the SA arm, with the majority of the decrease in 1-NA achieved by Day 1, followed by a further decrease and plateauing from Day 2 thereafter. Geometric mean 1-NA values decreased in the THS 2.2 Menthol arm from baseline (61.45 pg/mg creat) to Day 5 (3.14 pg/mg creat), whereas 1-NA values in the mCC arm had a baseline value of 57.24 pg/mg creat and Day 5 had a value of 53.27 pg/mg creat. These values corresponded to percent changes from baseline of -94.13 % and -3.64% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 1-NA values decreased from baseline (53.48 pg/mg creat) to Day 5 (2.85 pg/mg creat), as expected, which corresponded to a -93.49% change from baseline.

During the Ambulatory Period, geometric mean 1-NA values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (3.70, 3.36, and 3.55 pg/mg creat, respectively), but were higher than the Day 5 value. Mean 1-NA in the mCC arm



on Days 30, 60, and 90 was 49.94, 50.66, and 55.34 pg/mg creat, respectively. These values corresponded to percent changes from baseline on Day 90 of -92.01 and 7.68% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 1-NA values remained decreased from baseline, as expected, with a -86.11% change from baseline on Day 90 (4.22 pg/mg creat).

Analyses of 1-NA urinary concentration adjusted for creatinine and urinary quantity of 1-NA excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 74](#) and [Table 75](#).

**Table 74 Analysis of 1-NA versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	3.58	5.42	43.82	4.61, 6.36
	mCC	42	66.17			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	3.12	5.70	39.23	4.93, 6.59
	mCC	42	54.64			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	3.58	100.88	43.82	85.59, 118.91
	SA	39	3.55			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	3.12	104.70	39.23	90.26, 121.44
	SA	39	2.98			

Abbreviations: 1-NA = 1-aminonaphthalene; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 94.30% lower than that of subjects who continued to smoke mCC (95% CI: 93.41, 95.07; p-value <0.001). The results for the quantity of 1-NA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both 1-NA urinary concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 75 Analysis of 1-NA versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	3.89	6.43	82.29	4.85, 8.52
	mCC	41	60.52			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	3.55	6.22	81.42	4.70, 8.22
	mCC	41	57.11			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	3.89	79.91	82.29	59.75, 106.87
	SA	37	4.87			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	3.55	81.26	81.42	60.87, 108.47
	SA	37	4.37			

Abbreviations: 1-NA = 1-aminonaphthalene; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 93.78% lower than that of subjects who continued to smoke mCC (95% CI: 91.78, 95.30; p-value <0.001). The results for the quantity of 1-NA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both 1-NA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2



Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

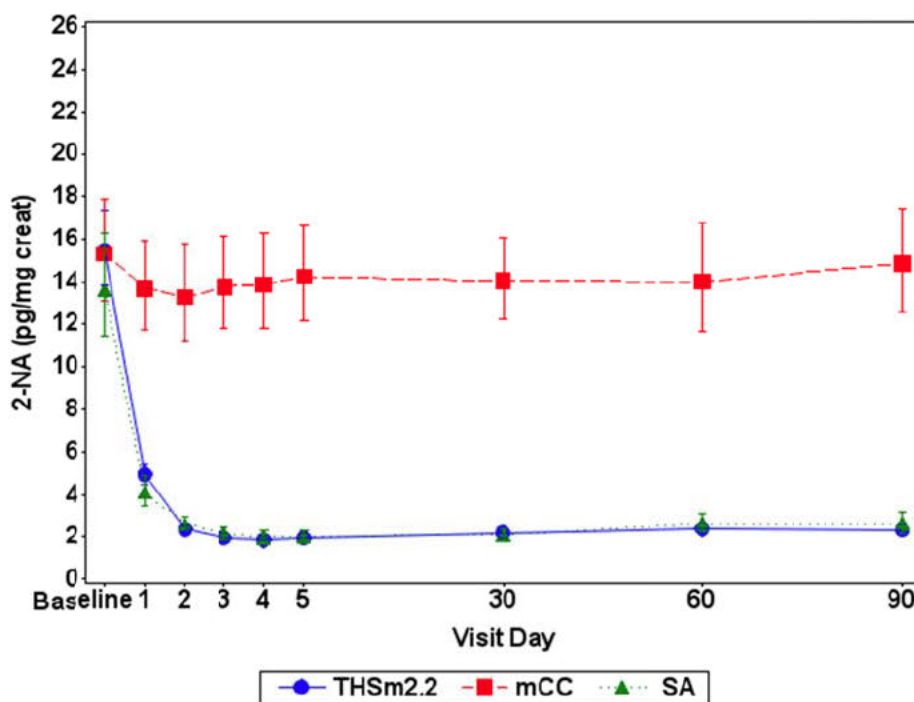
11.2.3.6 2-aminonaphthalene in 24-hour Urine During the Study

Subject listings of 2-NA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of 2-NA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.11.1](#) and [Table 15.2.4.11.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for 2-NA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 14](#).



Figure 14 Geometric Mean and 95% CI 2-NA Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 2-NA = 2-aminonaphthalene; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean 2-NA in the THS 2.2 Menthol arm was comparable to that of the SA arms, with a sharp decline on Day 1 and a further decrease observed on Day 2, before plateauing during thereafter. Geometric means of 2-NA decreased in the THS 2.2 Menthol study arm from baseline (15.49 pg/mg creat) to Day 5 (1.97 pg/mg creat), whereas 2-NA in the mCC arm had a baseline value of 15.32 pg/mg creat and a Day 5 value of 14.23 pg/mg creat. These values corresponded to percent changes from baseline of -85.26% and -4.74% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 2-NA values decreased from baseline (13.64 pg/mg creat) to Day 5 (2.04 pg/mg creat), as expected, which corresponded to a -83.02% change from baseline.

During the Ambulatory Period, geometric mean 2-NA values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (2.19, 2.37, and 2.34 pg/mg creat, respectively), but were higher than the Day 5 value. Mean 2-NA in the mCC arm on Days 30, 60, and 90 was 14.03, 14.00, and 14.84 pg/mg creat, respectively. These



values corresponded to percent changes from baseline on Day 90 of -81.75% and 6.31% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 2-NA values remained decreased from baseline, as expected, with a -74.09% change from baseline on Day 90 (2.63 pg/mg creat).

Analyses of 2-NA urinary concentration adjusted for creatinine and urinary quantity of 2-NA excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 76](#) and [Table 77](#).

**Table 76 Analysis of 2-NA versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			95% CI
				CV%			
Quantity excreted over 24 hours (ng)	THS m2.2	76	2.26	12.92	38.35	11.21, 14.87	
	mCC	42	17.53				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1.97	13.66	33.99	12.04, 15.49	
	mCC	42	14.43				

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			95% CI
				CV%			
Quantity excreted over 24 hours (ng)	THS m2.2	76	2.26	88.03	38.35	76.14, 101.77	
	SA	39	2.57				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1.97	91.67	33.99	80.53, 104.33	
	SA	39	2.15				

Abbreviations: 2-NA = 2-aminonaphthalene; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4.](#)

On Day 5, the LS mean of 2-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 86.34% lower than that of subjects who continued to smoke mCC (95% CI: 84.51, 87.96; p-value <0.001). The results for the quantity of 2-NA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both 2-NA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 77 Analysis of 2-NA versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	2.59	16.13	49.66	13.43, 19.37
	mCC	41	16.05			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	2.35	15.45	47.02	12.98, 18.39
	mCC	41	15.22			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	2.59	84.76	49.66	70.11, 102.47
	SA	37	3.05			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	2.35	85.50	47.02	71.35, 102.45
	SA	37	2.75			

Abbreviations: 2-NA = 2-aminonaphthalene; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of 2-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 84.55% lower than that of subjects who continued to smoke mCC (95% CI: 81.61, 87.02; p-value <0.001). The results for the quantity of 2-NA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both 2-NA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2



Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

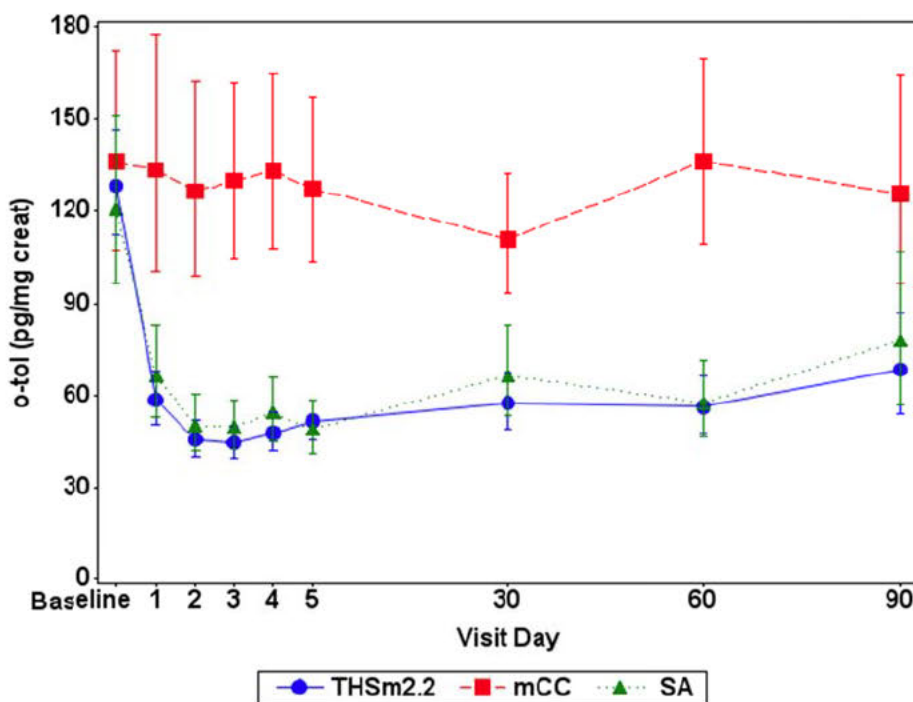
11.2.3.7 o-toluidine in 24-hour Urine During the Study

Subject listings of o-toluidine data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of o-toluidine adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.12.1](#) and [Table 15.2.4.12.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for o-toluidine urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 15](#).



Figure 15 Geometric Mean and 95% CI o-tol Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mCC = menthol conventional cigarettes; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: Appendix 15, Figure 15.1.1.2.

The profile of o-toluidine for the THSm2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Day 1 and a further decrease observed on Day 2, before remaining decreased from baseline. Geometric mean o-toluidine values decreased in the THSm2.2 Menthol arm from baseline (128.19 pg/mg creat) to Day 5 (51.64 pg/mg creat), whereas o-toluidine in the mCC arm had a baseline value of 136.04 pg/mg creat and a Day 5 of 127.28 pg/mg creat. These values corresponded to percent changes from baseline of -46.70% and -3.37% for the THSm2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean o-toluidine values decreased from baseline (120.54 pg/mg creat) to Day 5 (48.82 pg/mg creat), as expected, which corresponded to a -52.53% change from baseline.

During the Ambulatory Period, geometric mean o-toluidine values in the THSm2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (57.46, 57.15, and 68.35 pg/mg creat, respectively), but were higher than the Day 5 value. o-toluidine in the



mCC arm on Days 30, 60, and 90 was 110.84, 136.16, and 125.64 pg/mg creat, respectively). These values corresponded to percent changes from baseline on Day 90 of 31.91% and 13.69% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean o-toluidine values remained decreased from baseline, as expected, with a 1.94% change from baseline on Day 90 (77.86 pg/mg creat).

Analyses of o-toluidine urinary concentration adjusted for creatinine and urinary quantity of o-toluidine excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 78](#) and [Table 79](#).

**Table 78 Analysis of o-tol versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			95% CI
				LS Mean	CV%		
Quantity excreted over 24 hours (ng)	THS m2.2	76	59.98				
	mCC	40	144.15	41.61	51.21		34.42, 50.30
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	52.17				
	mCC	40	119.11	43.80	50.51		36.31, 52.83

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			95% CI
				LS Mean	CV%		
Quantity excreted over 24 hours (ng)	THS m2.2	76	59.98				
	SA	39	60.86	98.55	51.21		81.66, 118.93
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	52.17				
	SA	39	50.75	102.80	50.51		85.37, 123.79

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of o-toluidine concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 56.20% lower than that of subjects who continued to smoke mCC (95% CI: 47.17, 63.69; p-value <0.001). The results for the quantity of o-toluidine excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both o-toluidine urinary concentrations adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 79 Analysis of o-tol versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	77.95	61.96	100.63	44.26, 86.74
	mCC	40	125.80			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	69.75	59.16	102.96	42.02, 83.29
	mCC	40	117.90			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	77.95	88.35	100.63	63.12, 123.67
	SA	37	88.22			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	69.75	87.24	102.96	61.98, 122.80
	SA	37	79.95			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of o-toluidine concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 40.84% lower than that of subjects who continued to smoke mCC (95% CI: 16.71, 57.98; p-value = 0.001). The results for the quantity of o-toluidine excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both o-toluidine concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

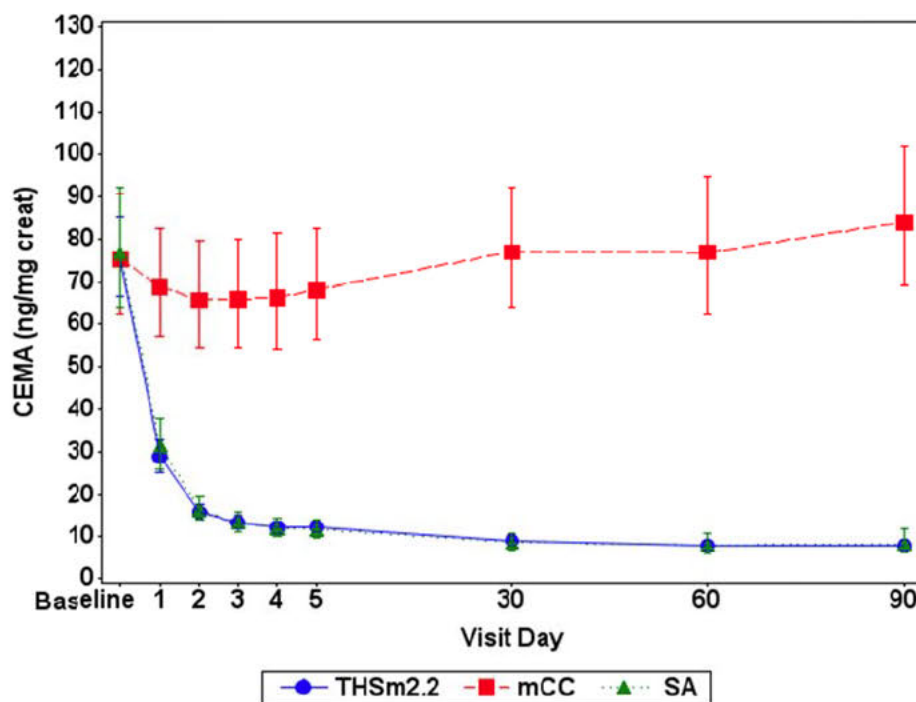
11.2.3.8 2-cyanoethylmercapturic acid in 24-hour Urine During the Study

Subject listings of CEMA are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of CEMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.13.1](#) and [Table 15.2.4.13.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for CEMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 16](#).



Figure 16 Geometric Mean and 95% CI CEMA Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of CEMA for the THS 2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Day 1 and a further decrease to Day 5. Geometric mean CEMA values decreased in the THS 2.2 Menthol arm from baseline (75.32 ng/mg creat) to Day 5 (12.43 ng/mg creat) whereas CEMA values in the mCC arm had a baseline value of 75.19 ng/mg creat and a Day 5 value of 68.17 ng/mg creat. These values correspond to percent changes from baseline of -82.39% and -5.18% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean CEMA values decreased from baseline (76.74 ng/mg creat) to Day 5 (12.43 ng/mg creat), as expected, which corresponded to a -83.70 % change from baseline.

During the Ambulatory Period, geometric mean CEMA values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (9.19, 7.84, and 7.91 ng/mg creat, respectively), lower than the Day 5 value. Mean CEMA in the mCC arm was greater than baseline on days 30, 60, and 90 (76.97, 76.89, and 83.98 ng/mg



creat, respectively). These values corresponded to percent changes from baseline on Day 90 of -86.31% and 21.70% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean CEMA values remained decreased from baseline, as expected, with a -79.89% change from baseline on Day 90 (8.41 ng/mg creat).

Analyses of CEMA urinary concentration adjusted for creatinine and urinary quantity of CEMA excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 80](#) and [Table 81](#).

**Table 80 Analysis of CEMA versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	76	14.35	17.10	36.94	14.92, 19.59
	mCC	42	83.94			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	76	12.43	18.23	32.43	16.16, 20.56
	mCC	42	68.18			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	76	14.35	102.15	36.94	88.87, 117.42
	SA	39	14.05			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	76	12.43	107.03	32.43	94.63, 121.05
	SA	39	11.61			

Abbreviations: ANCOVA = analysis of covariance; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4.](#)

On Day 5, the LS mean of CEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 81.77% lower than that of subjects who continued to smoke mCC (95% CI: 79.44, 83.84; p-value <0.001). The results for the quantity of CEMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both CEMA urinary concentrations adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 81 Analysis of CEMA versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	70	8.72	9.55	75.36	7.35, 12.40
	mCC	41	91.35			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	70	7.84	9.17	78.11	7.01, 12.00
	mCC	41	85.45			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	70	8.72	92.79	75.36	70.86, 121.50
	SA	37	9.40			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	70	7.84	91.93	78.11	69.65, 121.33
	SA	37	8.53			

Abbreviations: ANCOVA = analysis of covariance; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of CEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 90.83% lower than that of subjects who continued to smoke mCC (95% CI: 88.00, 92.99; p-value <0.001). The results for the quantity of CEMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both CEMA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

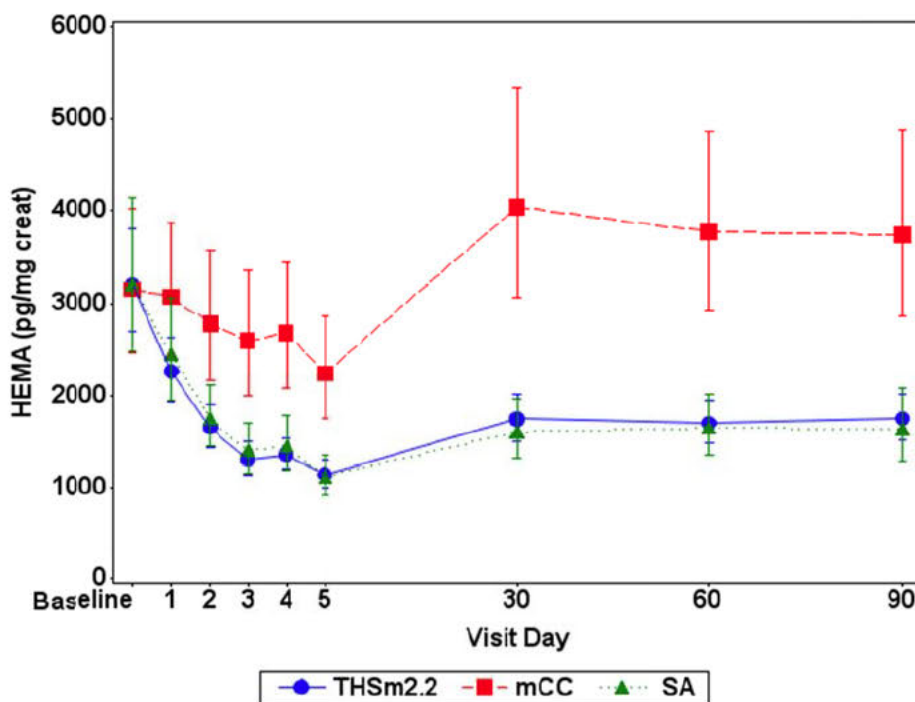
11.2.3.9 2-hydroxyethyl mercapturic Acid in 24-hour Urine During the Study

Subject listings of HEMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of HEMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.14.1](#) and [Table 15.2.4.14.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for HEMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 17](#).



Figure 17 Geometric Mean and 95% CI HEMA Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; HEMA = 2-hydroxyethyl mercapturic acid; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean HEMA in the THS 2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Days 1, 2, and 3, followed by a further decrease observed on Day 5. Geometric mean HEMA values decreased in the THS 2.2 Menthol arm from baseline (3203.95 pg/mg creat) to Day 5 (1137.96 pg/mg creat), whereas HEMA in the mCC arm had a baseline value of 3148.47 pg/mg creat and a Day 5 value of 2235.37 pg/mg creat. These values corresponded to percent changes from baseline of -61.14% and -26.60% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean HEMA values decreased from baseline (3201.31 pg/mg creat) to Day 5 (1113.73 pg/mg creat), as expected, which corresponded to a -61.24% change from baseline.

During the Ambulatory period, geometric mean HEMA values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (1739.46, 1694.19, and 1711.53 pg/mg creat, respectively), but were higher than the Day 5 value. Mean HEMA



in the mCC arm was greater than baseline on Days 30, 60, and 90 (4038.40, 3773.50, and 3739.46 pg/mg creat, respectively). These values corresponded to percent changes from baseline on Day 90 of -39.29% and 33.12% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean HEMA values remained decreased from baseline, as expected, with a -35.41% change from baseline on Day 90 (1633.12 pg/mg creat).

Analyses of HEMA urinary concentration adjusted for creatinine and urinary quantity of HEMA excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on during the study are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 82](#) and [Table 83](#).

**Table 82 Analysis of HEMA versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			95% CI
				CV%			
Quantity excreted over 24 hours (ng)	THS m2.2	76	1326.41	47.11	39.96		40.69, 54.54
	mCC	42	2815.66				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1145.94	50.14	34.79		44.09, 57.02
	mCC	42	2285.36				

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			95% CI
				CV%			
Quantity excreted over 24 hours (ng)	THS m2.2	76	1326.41	97.71	39.96		84.12, 113.50
	SA	39	1357.47				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	1145.94	102.15	34.79		89.55, 116.51
	SA	39	1121.87				

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; HEMA = 2-hydroxyethyl mercapturic acid; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of HEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 49.86% lower than that of subjects who continued to smoke mCC (95% CI: 42.98, 55.91; p-value <0.001). The results for the quantity of HEMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both HEMA urinary concentrations adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 83 Analysis of HEMA versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV%	95% CI
				(THS m2.2:mCC) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	70	1917.63	46.77	51.39	38.73, 56.48
	mCC	41	4099.99			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	1719.75	44.96	51.89	37.17, 54.37
	mCC	41	3825.31			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV%	95% CI
				(THS m2.2:SA) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	70	1917.63	103.15	51.39	84.91, 125.32
	SA	37	1859.03			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	1719.75	102.01	51.89	83.82, 124.15
	SA	37	1685.89			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; HEMA = 2-hydroxyethyl mercapturic acid; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of HEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 55.04% lower than that of subjects who continued to smoke mCC (95% CI: 45.63, 62.83; p-value <0.001). The results for the quantity of HEMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both HEMA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

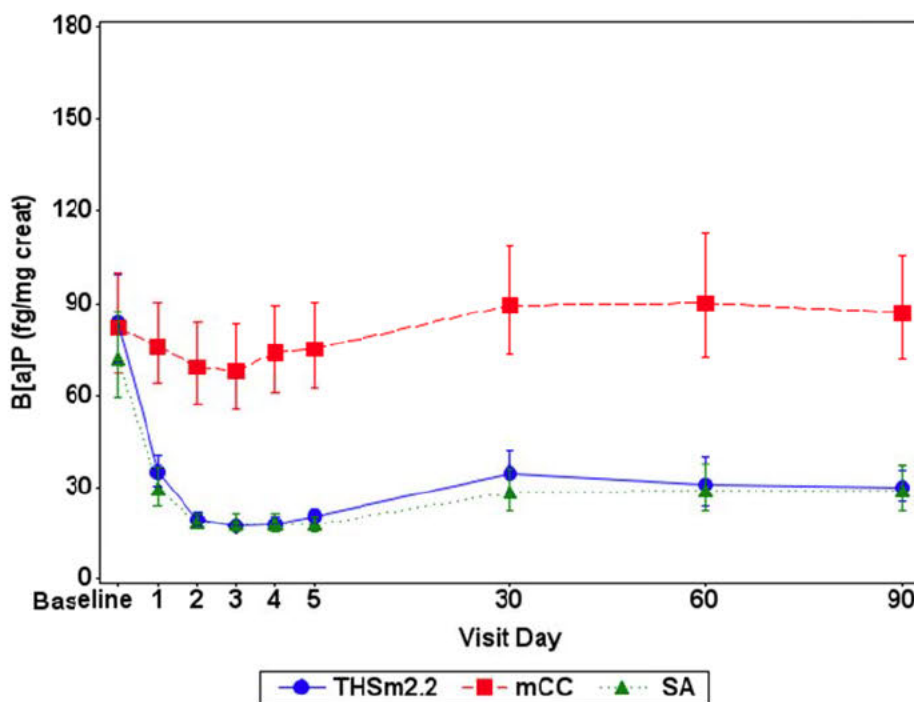
11.2.3.10 3-hydroxybenzo(a)pyrene in 24-hour Urine During the Study

Subject listings of B[a]P data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of B[a]P adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.15.1](#) and [Table 15.2.4.15.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for B[a]P urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 18](#).



Figure 18 Geometric Mean and 95% CI B[a]P Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: B[a]P = 3-hydroxybenzo(a)pyrene; CI = confidence interval; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean B[a]P in the THS 2.2 Menthol was comparable to that of the SA arm, with the majority of the decrease from baseline observed on Day 1. Geometric mean B[a]P values decreased in the THS 2.2 Menthol arm from baseline (83.73 fg/mg creat) to Day 5 (20.72 fg/mg creat), whereas B[a]P in the mCC arm had a baseline value of 82.00 fg/mg creat and a Day 5 value of 75.10 fg/mg creat. These values corresponded to percent changes from baseline of -68.42% and -3.79% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean B[a]P values decreased from baseline (71.96 fg/mg creat) to Day 5 (17.84 fg/mg creat), as expected, which corresponded to a -75.04% change from baseline.

During the Ambulatory period, geometric mean B[a]P values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (34.53, 30.93, and 30.92 fg/mg creat, respectively), but were higher than the Day 5 value. Mean B[a]P in the mCC arm was greater than baseline on Days 30, 60, and 90 (89.38, 90.12, and



86.92 fg/mg creat, respectively). These values corresponded to percent changes from baseline on Day 90 of -49.20% and 21.49% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean B[a]P values remained decreased from baseline, as expected, with a -46.51% change from baseline on Day 90 (28.88 fg/mg creat).

Analyses of B[a]P urinary concentration adjusted for creatinine and urinary quantity of B[a]P excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 84](#) and [Table 85](#).

**Table 84 Analysis of B[a]P versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			95% CI
				LS Mean	CV%		
Quantity excreted over 24 hours (pg)	THS m2.2	76	23.88				
	mCC	42	92.65	25.77	46.59		21.77, 30.51
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	76	20.79				
	mCC	42	76.46	27.19	43.93		23.17, 31.91

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			95% CI
				LS Mean	CV%		
Quantity excreted over 24 hours (pg)	THS m2.2	76	23.88				
	SA	39	22.43	106.45	46.59		89.51, 126.58
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	76	20.79				
	SA	39	18.80	110.59	43.93		93.84, 130.33

Abbreviations: ANCOVA = analysis of covariance; B[a]P = 3-hydroxybenzo(a)pyrene; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of B[a]P concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 72.81% lower than that of subjects who continued to smoke mCC (95% CI: 68.09, 76.83; p-value <0.001). The results for the quantity of B[a]P excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both B[a]P urinary concentrations adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 85 Analysis of B[a]P versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (pg)	THS m2.2	70	33.09	34.56	71.49	26.90, 44.40
	mCC	41	95.73			
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	70	29.83	33.02	68.71	25.92, 42.08
	mCC	41	90.33			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (pg)	THS m2.2	70	33.09	96.83	71.49	74.69, 125.54
	SA	37	34.17			
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	70	29.83	95.92	68.71	74.58, 123.38
	SA	37	31.10			

Abbreviations: ANCOVA = analysis of covariance; B[a]P = 3-hydroxybenzo(a)pyrene; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.
Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of B[a]P concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 66.98% lower than that of subjects who continued to smoke mCC (95% CI: 57.92, 74.08; p-value <0.001). The results for the quantity of B[a]P excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both B[a]P concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

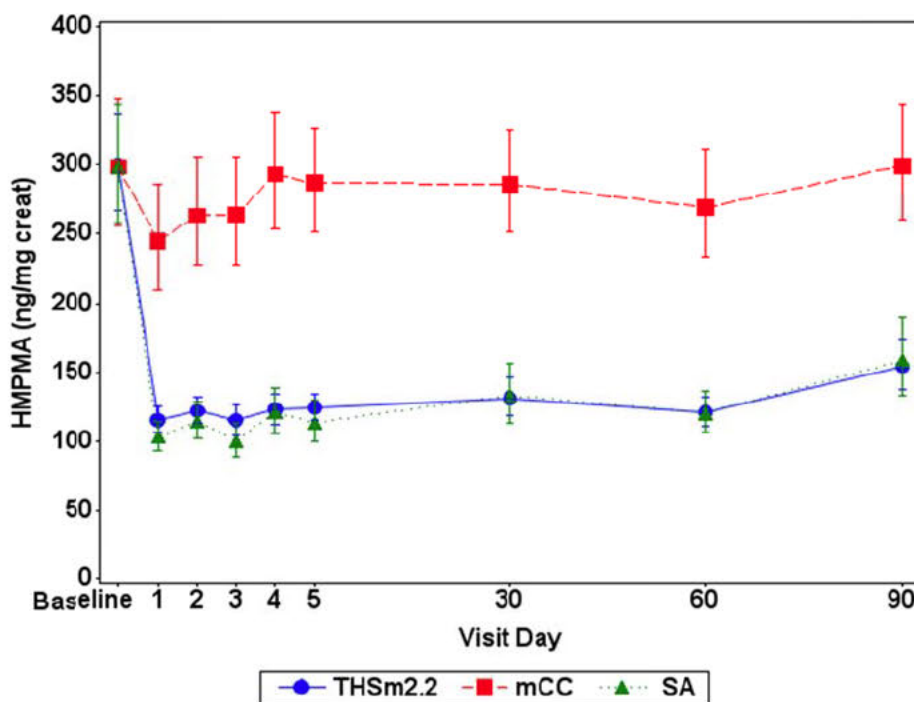
11.2.3.11 3-hydroxy-1-methylpropyl-mercapturic acid in 24-hour Urine During the Study

Subject listings of HMPMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of HMPMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.16.1](#) and [Table 15.2.4.16.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for HMPMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 19](#).



Figure 19 Geometric Mean and 95% CI HMPMA Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean HMPMA for the THSm2.2 menthol arm was comparable to that of the SA arm, with the majority of the reduction achieved on Day 1, before plateauing thereafter. Geometric mean HMPMA values decreased in the THSm2.2 Menthol arm from baseline (300.07 ng/mg creat) to Day 5 (124.47 ng/mg creat), whereas HMPMA values in the mCC arms had a baseline value of 298.73 ng/mg creat and a Day 5 of 286.80 ng/mg creat. These values corresponded to percent changes from baseline of -50.77% and 0.27% for the THSm2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean HMPMA values decreased from baseline (298.08 ng/mg creat) to Day 5 (113.48 ng/mg creat), as expected, which corresponded to a -54.44% change from baseline.

During the Ambulatory Period, geometric mean HMPMA values in the THSm2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (131.25, 121.00, and 151.30 ng/mg creat, respectively), whereas HMPMA in the mCC arm on Days 30, 60, and 90 was 286.13, 269.06, and 299.41 ng/mg creat, respectively. These values



corresponded to percent changes from baseline on Day 90 of -33.72% and 15.67% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean HMPMA values remained decreased from baseline, as expected, with a -26.90% change from baseline on Day 90 (158.57 ng/mg creat).

Analyses of HMPMA urinary concentration adjusted for creatinine and urinary quantity of HMPMA excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 86](#) and [Table 87](#).

**Table 86 Analysis of HMPMA versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	76	144.79	40.82	38.93	35.38, 47.09
	mCC	42	354.72			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	76	126.41	43.06	35.59	37.75, 49.10
	mCC	42	293.61			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	76	144.79	104.80	38.93	90.54, 121.31
	SA	39	138.15			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	76	126.41	109.54	35.59	95.76, 125.30
	SA	39	115.40			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of HMPMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 56.94% lower than that of subjects who continued to smoke mCC (95% CI: 50.90, 62.25; p-value <0.001). The results for the quantity of HMPMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both HMPMA urinary concentrations adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 87 Analysis of HMPMA versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	70	175.12	52.32	49.42	43.60, 62.79
	mCC	41	334.68			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	70	158.99	50.31	42.22	42.96, 58.91
	mCC	41	316.01			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	70	175.12	95.53	49.42	79.15, 115.29
	SA	37	183.32			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	70	158.99	95.90	42.22	81.47, 112.89
	SA	37	165.78			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS mean of HMPMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 49.69% lower than that of subjects who continued to smoke mCC (95% CI: 41.09, 57.04; p-value <0.001). The results for the quantity of HMPMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both HMPMA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

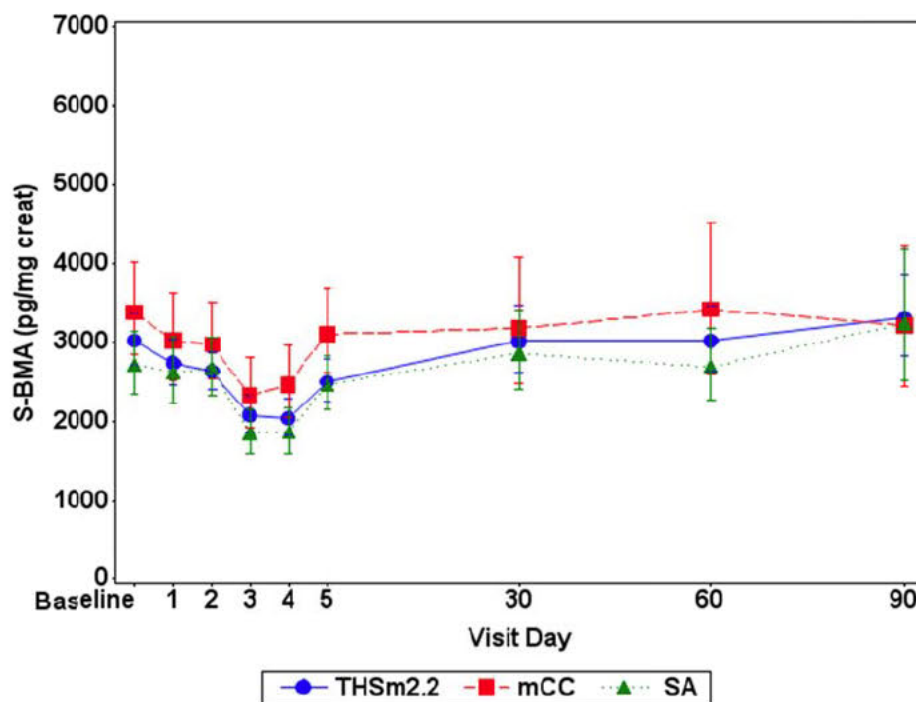
11.2.3.12 S-benzylmercapturic Acid in 24-hour Urine During the Study

Subject listings of S-BMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of S-BMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in [Appendix 15, Table 15.2.4.17.1](#) and [Table 15.2.4.17.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for S-BMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 20](#).



Figure 20 Geometric Mean and 95% CI S-BMA Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; THSm2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profiles of mean S-BMA values were generally similar for all study arms, with mean values decreasing from baseline to Day 4 for all treatment groups. Geometric mean S-BMA values in the THSm2.2 Menthol, mCC, and SA arms decreased from baseline (3026.36, 3383.70, and 2718.95 pg/mg creat, respectively) to Day 5 (2503.48, 3108.11, and 2471.21 pg/mg creat, respectively), which corresponded to percent changes from baseline on Day 5 of -11.45%, -4.41%, and -4.49% for the THSm2.2 Menthol, mCC, and SA arms, respectively.

During the Ambulatory Period, geometric mean S-BMA values were also similar for all study arms, with mean values in the THSm2.2 Menthol arm on Days 30, 60, and 90 of 3017.49, 3022.87, and 3314.09 pg/mg creat, respectively. Mean S-BMA in the mCC arm on Days 30, 60, and 90 were 3180.76, 3420.00, and 3221.80 pg/mg creat, respectively. These values corresponded to percent changes from baseline on Day 90 of 23.73% and 54.48% for the THSm2.2 Menthol and mCC arms, respectively. In the SA arm, geometric



mean S-BMA values on Days 30, 60, and 90 were 2861.17, 2691.71, and 3249.02, respectively, with a 75.30% change from baseline on Day 90.

Analyses of S-BMA urinary concentration adjusted for creatinine and urinary quantity of S-BMA excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 88](#) and [Table 89](#).

Table 88 Analysis of S-BMA versus mCC and SA on Day 5 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV%	95% CI
				(THS m2.2:mCC) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	76	2942.90	79.99	38.51	69.40, 92.19
	mCC	42	3679.22			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	2547.36	85.83	30.78	76.49, 96.31
	mCC	42	2967.89			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV%	95% CI
				(THS m2.2:SA) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	76	2942.90	91.18	38.51	78.83, 105.45
	SA	39	3227.72			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	2547.36	94.56	30.78	84.06, 106.38
	SA	39	2693.82			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 5, the LS mean of S-BMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 14.17% lower than that of subjects who continued



to smoke mCC (95% CI: 3.69, 23.51; p-value = 0.005). The results for the quantity of S-BMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both S-BMA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.


Table 89 Analysis of S-BMA versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			95% CI
				CV%			
Quantity excreted over 24 hours (ng)	THS m2.2	70	3742.58	115.95	64.43		92.10, 145.96
	mCC	41	3227.88				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	3335.21	111.27	63.33		88.65, 139.67
	mCC	41	2997.27				

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			95% CI
				CV%			
Quantity excreted over 24 hours (ng)	THS m2.2	70	3742.58	92.75	64.43		73.11, 117.65
	SA	37	4035.26				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	3335.21	91.73	63.33		72.53, 116.01
	SA	37	3635.94				

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Data Source: [Appendix 15, Table 15.2.3.4](#).

On Day 90, the LS means of S-BMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 11.27% higher than that of subjects who continued to smoke mCC (95% CI: -11.35, 39.67). The results for the quantity of S-BMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both S-BMA concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

11.2.4 Biomarkers of Exposure to Nicotine During the Study

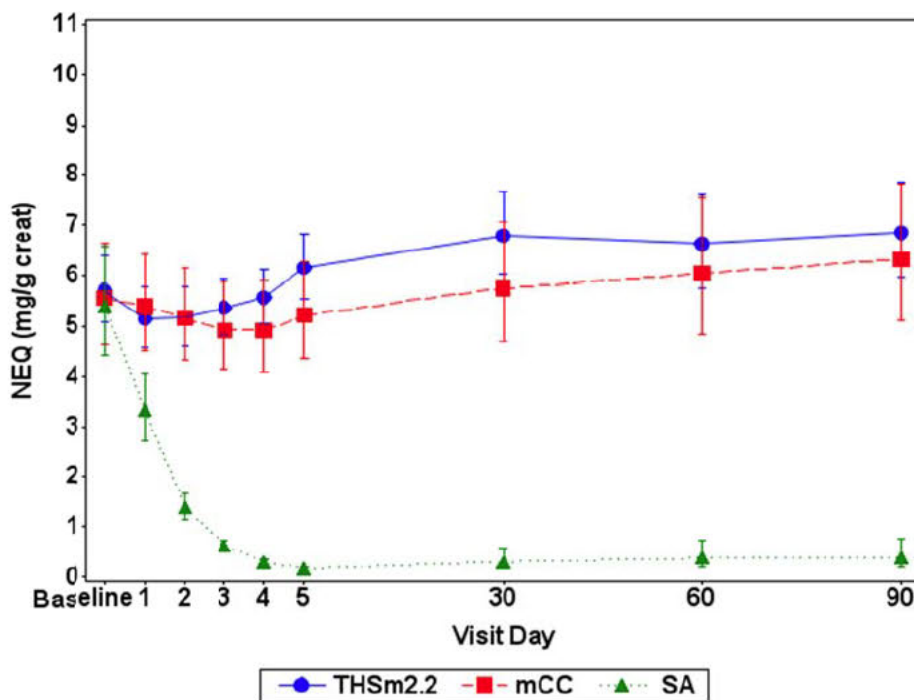
11.2.4.1 Nicotine Equivalents in 24-hour Urine During the Study

Subject listings of NEQ data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of the concentration of NEQ adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.18.1](#) and [Table 15.2.4.18.2](#) together with changes from baseline for the PP Set and FAS, respectively. Geometric mean and 95% CIs for NEQ urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also provided in [Figure 21](#).



Figure 21 Geometric Mean and 95% CI Urinary IEQ Quantity Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mC = menthol conventional cigarettes; NEQ = nicotine equivalents; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of mean NEQ in the THS 2.2 Menthol arm was comparable to that of the mCC arm. Geometric mean NEQ values at baseline, Day 1, and Day 5 were 5.71, 5.15, and 6.16 mg/g creat, respectively, for the THS 2.2 Menthol arm, and 5.56, 5.40, and 5.22 mg/g creat, respectively, for the mCC arm. An initial decrease from baseline was observed in the THS 2.2 Menthol arm, with percent changes from baseline at Day 1 of -6.26% and -0.76% for the THS 2.2 Menthol and mCC arms respectively. On Day 5 percent changes from baseline for the THS 2.2 Menthol and mCC were of 16.00% and -3.30%, respectively. In contrast, in the SA arm, geometric mean NEQ values decreased from baseline (5.40 mg/g creat) to Day 5 (0.16 mg/g creat), as expected, corresponding to a -96.21% change from baseline.

During the Ambulatory Period, the profile of mean NEQ in the THS 2.2 Menthol arm was comparable to that of the mCC arm. Geometric mean NEQ values in the THS 2.2 Menthol arm on Days 30, 60, and 90 were 6.81, 6.63, and 6.85 mg/g creat, respectively,



and in the mCC arm values were 5.76, 6.05, and 6.33 mg/g creat, respectively. These values corresponded to percent changes from baseline on Day 90 of 36.47% and 25.83% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, NEQ values remained decreased from baseline, as expected, with a -58.18% change from baseline on Day 90 (0.37 mg/g creat).

Analyses of NEQ urinary concentration adjusted for creatinine and urinary quantity of NEQ excreted over 24 hours for THS 2.2 Menthol users versus mCC use, and versus SA on Day 5 are tabulated in [Appendix 15, Table 15.2.3.4](#) and [15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis on the Compliant Population and analysis using a mixed model on the PP Set were performed and are tabulated in [Appendix 15, Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also provided in [Table 90](#) and [Table 91](#).

Table 90 Analysis of NEQ versus mCC on Day 5 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (mg)	THS m2.2	76	7.00	109.18	46.28	92.33, 129.10
	mCC	42	6.41			
Concentration adjusted for creatinine (mg/g creat)	THS m2.2	76	6.06	116.00	43.83	98.91, 136.04
	mCC	42	5.23			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; NEQ = nicotine equivalents; PP = per protocol; THS 2.2 = Tobacco Heating System 2.2.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline values, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.3.4](#)

On Day 5, both NEQ urinary concentration adjusted for creatinine and quantity excreted over 24 hours was approximately 16% and 9% higher, respectively, in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC. The 95% CIs for the THS 2.2 Menthol and mCC ratio of both assessments spanned 100%; with the ratio approximately ranging between 99% and 136% for the assessment adjusted by creatinine.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

**Table 91 Analysis of NEQ versus mCC on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (mg)	THS m2.2	70	7.54	108.39	157.78	70.13, 167.51
	mCC	41	6.96			
Concentration adjusted for creatinine (mg/g creat)	THS m2.2	70	6.75	104.30	165.93	66.65, 163.20
	mCC	41	6.47			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; NEQ = nicotine equivalents; PP = per protocol; THS 2.2 = Tobacco Heating System 2.2.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline values, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.3.4](#)

On Day 90, no notable differences in LS means were observed for either NEQ urinary concentration adjusted for creatinine and quantity excreted over 24 hours between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

11.2.4.2 Nicotine and Cotinine Concentrations in Plasma During the Study

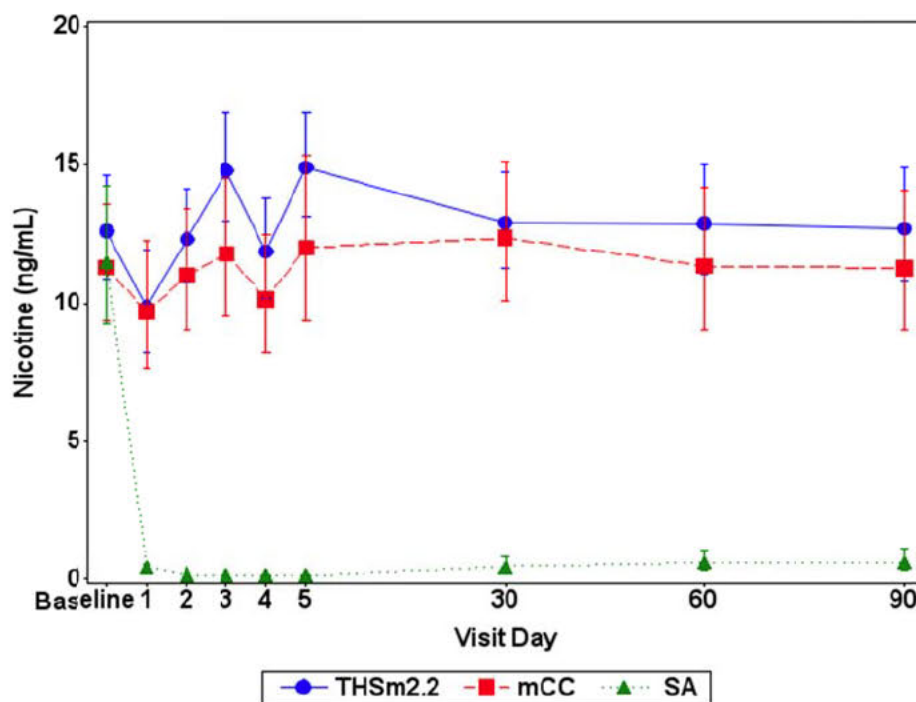
11.2.4.2.1 Plasma Nicotine Concentrations and PK Parameters

Plasma nicotine concentrations (ng/mL) and sampling times are listed by subject in [Appendix 15, Listing 15.3.3.3](#). Plasma nicotine concentrations are summarized by study arm in [Appendix 15, Table 15.2.4.19.1](#) and [15.2.4.19.2](#) for the PP Set and FAS, respectively.

Geometric mean and 95% CIs concentrations are shown by study arm in [Appendix 15, Figure 15.1.2.1.1](#) and [15.1.2.1.2](#) for the PP Set and FAS. Data for the PP Set are also presented in [Figure 22](#).



Figure 22 Geometric Mean and 95% CI Plasma Nicotine Concentrations (ng/mL) (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

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

Geometric mean plasma nicotine concentration profiles for samples taken between 08:00 and 09:30 PM were similar for the THS 2.2 menthol and mCC arms at baseline (12.60 and 11.27 ng/mL, respectively). During the Confinement Period, the profiles for THS 2.2 Menthol and mCC were variable and fluctuating, with mean nicotine values on Day 5 (T0+12h) of 15.86 and 11.98 ng/mL, respectively. In the SA arm, the mean nicotine concentration was comparable to the other study arms at baseline (11.47 ng/mL) before decreasing to 0.38 ng/mL on Day 1, where concentrations remained decreased or BLOQ for the remainder of the Confinement Period. The number (percentage) of BLOQ values for the SA arm increased from 0 on Day 1 to 38 (97.4%) on Day 5, compared to ≤1 BLOQ values in the THS 2.2 Menthol or mCC arm from Days 1 to 4.

During the Ambulatory Period, geometric mean nicotine concentrations on Days 30, 60, and Day 90 remained similar and stable for the THS 2.2 Menthol and mCC arms, with Day 90 mean concentrations of 12.69 and 11.25 ng/mL, respectively. In the SA arm, the



mean concentrations of nicotine during the Ambulatory Period remained decreased from baseline to Day 90 (0.57 ng/mL).

Analysis of the plasma nicotine concentration from samples taken during the study is tabulated in [Appendix 15, Table 15.2.4.20.1](#) and [15.2.4.20.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 92](#) and [Table 93](#).

Table 92 Analysis of Plasma Nicotine Concentration at 08:00 PM on Day 5 (PP Set)

Variable (unit)	Exposure	Number of Subjects	LS Mean	THS m2.2:mCC Ratio (%)	95% CI
Nicotine	THS m2.2	66	14.00	110.37	92.09, 132.27
(ng/mL)	mCC	36	12.69		

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Geometric CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.20.1](#).

On Day 5, the LS mean of nicotine concentrations were approximately 10% higher in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC; however, the 95% CIs span 100%.

**Table 93 Analysis of Change from Baseline for Plasma Nicotine Concentration During the Ambulatory Period (PP Set)**

Exposure	Day	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	95% CI
				(THS m2.2:mCC) (%)	
THS m2.2	30	74	12.61	96.03	79.68, 115.74
mCC		41	13.13		
THS m2.2	60	71	12.68	102.81	82.87, 127.54
mCC		41	12.33		
THS m2.2	90	69	12.39	103.39	82.66, 129.30
mCC		41	11.98		

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometric CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.20.1](#).

On Days 30, 60, and 90, there were no notable differences in LS means of plasma nicotine concentrations between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CIs spanning 100%.

Subject listings of plasma nicotine concentration parameters on Day 5 are provided in [Appendix 15, Listing 15.3.3.4](#) and are summarized by study arm in [Appendix 15, Tables 15.2.4.21.1 and Table 15.2.4.21.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also tabulated in [Table 94](#).

**Table 94 Summary of Plasma Nicotine Concentration Parameters on Day 5 (PP Set)**

Parameter (unit)	THS m2.2 (N=76)	mCC (N=42)
C_{peak} (ng/mL)		
Number of subjects	76	41
Geometric mean	20.70	15.67
95% CI	18.38, 23.32	13.03, 18.86
Min, Max	2.8, 49.9	3.1, 41.4
CV (%)	55.75	63.83
t_{peak} (h)		
Number of subjects	76	41
Median	12.00	12.00
Min, Max	2.0, 16.0	4.0, 16.0
C_{avg} (ng/mL)		
Number of subjects	76	41
Geometric mean	11.20	8.72
95% CI	9.81, 12.80	7.01, 10.85
Min, Max	1.4, 34.9	1.2, 22.7
CV (%)	63.43	78.07

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; N = number of subjects; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol; t_{peak} = time to peak concentration.

Data Source: [Appendix 15, Table 15.2.4.21.1](#)

Analysis of the plasma nicotine concentration parameters on Day 5 is tabulated in [Appendix 15, Table 15.2.4.22.1](#) and [Table 15.2.4.22.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also tabulated in [Table 95](#).

**Table 95 Analysis of Plasma Nicotine Concentration PK Parameters on Day 5 (PP Set)**

Parameter (unit)	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS m2.2:mCC)	CV (%)	95% CI
				(%)		
C_{avg}^1 (ng/mL)	THS m2.2	76	11.08	126.96	64.26	101.27, 159.15
	mCC	41	8.73			
C_{peak}^1 (ng/mL)	THS m2.2	76	20.57	130.66	55.86	106.93, 159.64
	mCC	41	15.74			

Parameter (unit)	Exposure	Number of Subjects	Median (h)	Median Difference	95% CI
				(h)	
t_{peak}^2 (h)	THS m2.2	76	12.00	-1.0	-2.00, 0.00
	mCC	41	12.00		

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; PK = pharmacokinetic; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol; t_{peak} = time to peak concentration.

¹ Geometric LS mean and 95% CI are the adjusted geometric least squares means based on a mixed model conducted on log-transformed values Day 5 values with study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

² 95% CI are estimated only for the median difference based on the Hodges-Lehmann estimate.

Data Source: [Appendix 15, Table 15.2.4.22.1](#).

For nicotine exposure on Day 5, peak and weighted average plasma concentrations were approximately 31% and 27% greater for the THS 2.2 Menthol arm compared to mCC arm, respectively, with corresponding 95% CIs of 106.93, 159.64 and 101.27, 159.15, respectively. The median time to peak concentration on Day 5 was similar for the THS 2.2 Menthol and mCC arms.

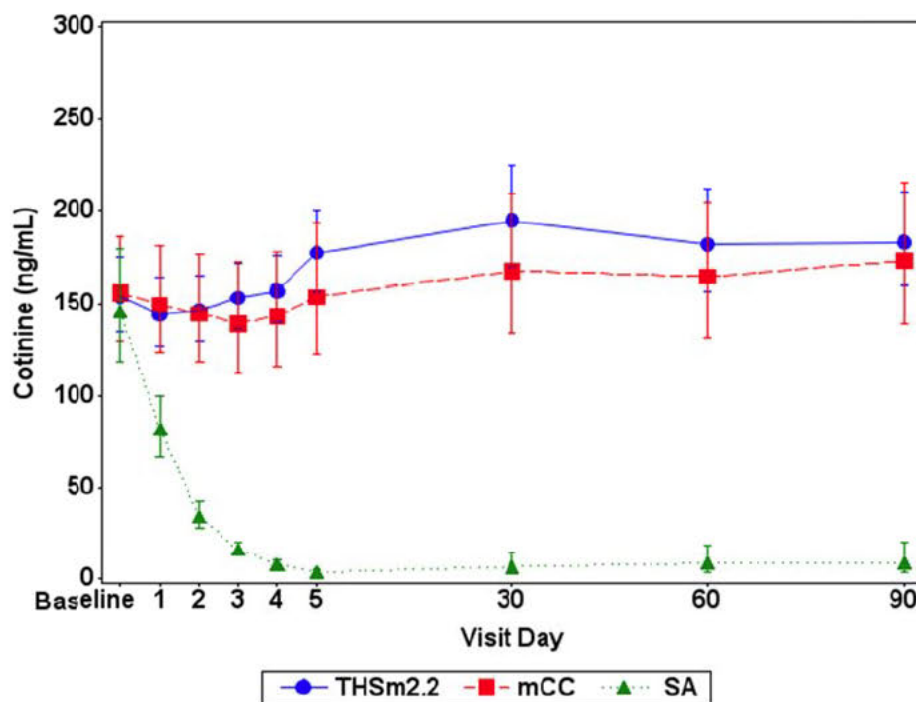
11.2.4.2.2 Plasma Cotinine Concentrations and PK Parameters

Plasma cotinine concentrations (ng/mL) and sampling times are listed by subject in [Appendix 15, Listing 15.3.3.3](#). Plasma cotinine concentrations are summarized by study arm in [Appendix 15, Table 15.2.4.19.1](#) and [15.2.4.19.2](#) for the PP Set and FAS, respectively.

Geometric mean and 95% CIs plasma cotinine concentrations are shown by study arm in [Appendix 15, Figure 15.1.2.1.1](#) and [15.1.2.1.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also presented in [Figure 23](#).



Figure 23 Geometric Mean and 95% CI Plasma Cotinine Concentrations (ng/mL) (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Baseline was defined as the last assessment prior to first randomized product use in mCC/THS 2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.
Baseline is summarized using the baseline data from the PP Set for Period 1.
Data Source: [Appendix 15](#), [Figure 15.1.2.1.1](#).

Geometric mean plasma cotinine concentration profiles for samples taken between 08:00 and 09:30 PM were similar for the THS 2.2 Menthol and mCC arm at baseline (153.65 and 155.44 ng/mL, respectively). On Day 5 (T0 +12h), concentrations of cotinine were 182.80 and 155.23 ng/mL in the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean cotinine concentrations were similar to those of the other study arms at baseline (145.26 ng/mL) before decreasing from baseline to 3.41 ng/mL on Day 5. The number (percentage) of BLOQ values for the SA arm was [10.3%] on Day 5.

During the Ambulatory Period, geometric mean cotinine concentrations for the THS 2.2 Menthol and mCC arms on Days 30, 60, and 90 were 194.86, 181.91, and 183.16 ng/mL for the THS 2.2 Menthol arm and 167.30, 164.23, and 172.69 ng/mL for the mCC arm. In the SA arm, the mean concentrations of cotinine during the Ambulatory Period remained decreased from baseline on Day 90 (3.49 ng/mL).



Analysis of the plasma cotinine concentration from samples taken during the study is tabulated in [Appendix 15, Table 15.2.4.20.1](#) and [15.2.4.20.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 96](#) and [Table 97](#).

Table 96 Analysis of Plasma Cotinine Concentration at 08:00 PM on Day 5 (PP Set)

Variable (unit)	Exposure	Number of Subjects	LS Mean	THS m2.2:mCC Ratio (%)	95% CI
Cotinine (ng/mL)	THS m2.2	66	176.16	111.63	99.87, 124.77
	mCC	36	157.81		

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Geometric CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.20.1](#).

On Day 5, the LS mean of cotinine concentrations were approximately 12% higher in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, although the lower 95% CI was lower than 100% at 99.87%.

Table 97 Analysis of Change from Baseline for Plasma Cotinine Concentration During the Ambulatory Period (PP Set)

Exposure	Day	Number of Subjects	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	95% CI
THS m2.2	30	74	196.40	114.46 97.00, 135.05
mCC		41	171.59	
THS m2.2	60	71	182.83	106.42 89.37, 126.73
mCC		41	171.80	
THS m2.2	90	69	185.81	105.94 89.89, 124.84
mCC		41	175.39	

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometric CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.20.1](#).

On Day 30, the LS mean cotinine concentrations were approximately 15% higher in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC; but the 95% CI spanned 100%.



On Days 60 and 90, there were no notable differences in LS means of plasma cotinine concentrations between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CIs spanning 100%.

Subject listings of plasma cotinine concentration parameters on Day 5 are provided in [Appendix 15, Listing 15.3.3.4](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.21.1](#) and [Table 15.2.4.21.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also tabulated in [Table 98](#).

Table 98 Summary of Plasma Cotinine Concentration Parameters on Day 5 (PP Set)

Parameter (unit)	THS m2.2 (N=76)	mCC (N=42)
C_{peak} (ng/mL)		
Number of subjects	76	41
Geometric mean	192.10	163.42
95% CI	171.50, 215.18	131.73, 202.73
Min, Max	38.3, 372.0	30.5, 427.0
CV (%)	52.85	77.07
t_{peak} (h)		
Number of subjects	76	41
Median	16.00	16.00
Min, Max	0.0, 24.0	0.0, 24.1
C_{avg} (ng/mL)		
Number of subjects	76	41
Geometric mean	171.25	147.39
95% CI	152.83, 191.90	118.72, 182.98
Min, Max	35.9, 322.5	28.3, 390.4
CV (%)	53.06	77.41

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; N = number of subjects; PK = Pharmacokinetic; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol; t_{peak} = time to peak concentration.

Data Source: [Appendix 15, Table 15.2.4.21.1](#)

Analysis of the plasma cotinine concentration parameters on Day 5 is tabulated in [Appendix 15, Table 15.2.4.22.1](#) and [Table 15.2.4.22.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also tabulated in [Table 99](#).

**Table 99 Analysis of Plasma Cotinine Concentration PK Parameters on Day 5 (PP Set)**

Parameter (unit)	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS m2.2:mCC)	CV (%)	95% CI
				(%)		
C_{avg}^1 (ng/mL)	THS m2.2	76	168.65	115.54	58.61	93.75, 142.38
	mCC	41	145.97			
C_{peak}^1 (ng/mL)	THS m2.2	76	189.25	116.95	58.71	94.87, 144.17
	mCC	41	161.82			

Parameter (unit)	Exposure	Number of Subjects	Median	Median Difference	95% CI
t_{peak}^2 (h)	THS m2.2	76	16.0	-2.0	-4.00, 0.00
	mCC	41	16.0		

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; PK = pharmacokinetic; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol; t_{peak} = time to peak concentration.

¹ Geometric LS mean and 95% CI are the adjusted geometric least squares means based on a mixed model conducted on log-transformed values Day 5 values with study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

² 95% CI are estimated only for the median difference based on the Hodges-Lehmann estimate.

Data Source: [Appendix 15, Table 15.2.4.22.1](#).

For cotinine exposure on Day 5, peak and weighted average plasma concentrations were approximately 17% and 16% higher, respectively, for the THS 2.2 Menthol arm compared to the mCC arm; however, the 95% CIs spanned 100% for both parameters. The median time to peak concentration on Day 5 was 16.0 hours for the THS 2.2 Menthol and mCC arms.

11.2.4.3 Cytochrome P450 1A2 Activity During the Study

Cytochrome P450 1A2 activity was calculated in plasma as the metabolic molar ratio of PX/CAF.

Individual subject listings of CYP1A2 activity and changes from baseline data are provided in [Appendix 15, Listing 15.3.4.1](#). Descriptive statistics of CYP1A2 activity including change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.23.1](#) and [Table 15.2.4.23.2](#) for the PP Set and FAS, respectively. In addition, descriptive statistics excluding any assessments taken within 5 half-lives of a concomitant medication known to impact CYP1A2 activity were summarized in [Appendix 15, Table 15.2.4.23.1.1](#) and [Table 15.2.4.23.2.1](#) for the PP Set and FAS, respectively.



Data for the PP Set are also provided in [Table 100](#) and [Table 101](#).

Table 100 Descriptive Statistics of Percent Change from Baseline in CYP1A2 Activity (%) During the Confinement Period (PP Set)

Study Arm	Time Point	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS m2.2	Day 5 % change from baseline	76	-21.75	15.250	-52.1	-21.79	16.4
mCC	Day 5 % change from baseline	42	9.65	23.145	-32.2	6.53	114.2
SA	Day 5 % change from baseline	39	-23.81	16.642	-46.8	-26.20	34.3

Abbreviations: CYP1A2 = Cytochrome P450 1A2; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

% change from baseline, where baseline was defined as Day 0.

Data Source: [Appendix 15, Table 15.2.4.23.1](#).

Table 101 Descriptive Statistics of Percent Change from Baseline in CYP1A2 Activity (%) During the Ambulatory Period (PP Set)

Study Arm	Time Point	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS m2.2	Day 90 % change from baseline	70	-20.22	26.983	-75.3	-20.70	71.1
mCC	Day 90 % change from baseline	41	15.77	39.676	-42.1	8.23	196.7
SA	Day 90 % change from baseline	37	-15.82	22.066	-63.1	-17.93	36.7

Abbreviations: CYP1A2 = Cytochrome P450 1A2; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

% change from baseline, where baseline was defined as Day 0.

Data Source: [Appendix 15, Table 15.2.4.23.1](#)

At baseline, CYP1A2 activity was similar between study arms, with mean values of 72.43%, 70.45%, and 74.18% for the THS 2.2 Menthol, mCC, and SA arms, respectively. In the THS 2.2 Menthol and SA arms, CYP1A2 activity decreased by 21.75% and 23.81%, respectively on Day 5. In the mCC arm, CYP1A2 activity increased by 9.65%. No assessments within the Confinement Period were within 5 half-lives of a post-randomization medication that could affect CYP1A2 activity.



At baseline, CYP1A2 activity was similar between study arms, with mean values of 72.51%, 70.17%, and 73.12% for the THS 2.2 Menthol, mCC, and SA arms, respectively (baseline values of the PP Set for Period 4). In the THS 2.2 Menthol and SA arms, CYP1A2 activity decreased by 20.22% and 15.82%, respectively on Day 90. In the mCC arm, CYP1A2 activity had increased by 15.77%. The analysis excluding assessments within 5 half-lives of post-randomization medications that impact CYP1A2 activity showed consistent results, with only 1 assessment excluded from the THS 2.2 Menthol arm.

Analyses of CYP1A2 activity (Day 5) for THS 2.2 Menthol use versus mCC use, and versus SA, are tabulated in [Appendix 15, Table 15.2.4.24.1](#) and [Table 15.2.4.24.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 102](#) and [Table 103](#).

Table 102 Analysis of CYP1A2 Activity (%) versus mCC and SA on Day 5 (PP Set)

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS m2.2:mCC) (%)	CV%	95% CI
THS m2.2	76	55.21	71.96	18.46	67.12, 77.16
mCC	42	76.72			

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS m2.2:SA) (%)	CV%	95% CI
THS m2.2	76	55.21	102.43	18.46	95.38, 110.00
SA	39	53.90			

Abbreviations: CI = confidence interval; CV = coefficient of variation; CYP1A2 = Cytochrome P450 1A2; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from a mixed model with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometric CV% of the ratio was estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.24.1](#)

On Day 5, the LS means of CYP1A2 activity following THS 2.2 Menthol use was 28.04% lower than in subjects who continued to smoke mCC (95% CI: 22.84, 32.88; p-value <0.001).



The LS means of CYP1A2 on Day 5 were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs spanning 100%.

Table 103 Analysis of CYP1A2 Activity (%) versus mCC and SA on Day 90 (PP Set)

Exposure	Number of Subjects	Geometric LS Mean	THS m2.2: mCC Ratio (%)	CV%	95% CI
THS m2.2	70	53.94	69.09	30.74	61.45, 77.68
mCC	41	78.07			

Exposure	Number of Subjects	Geometric LS Mean	THS m2.2: mCC Ratio (%)	CV%	95% CI
THS m2.2	70	53.94	92.48	30.74	81.95, 104.35
SA	37	58.33			

Abbreviations: CI = confidence interval; CV = coefficient of variation; CYP1A2 = Cytochrome P450 1A2; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometric CV% of the ratio was estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.24.1](#)

On Day 90, the LS means of CYP1A2 activity following THS 2.2 Menthol use was 30.91% lower than in subjects who continued to smoke mCC (95% CI: 22.32, 38.55; p-value <0.001). The exclusion of 1 assessment, which was within 5 half-lives of a post-randomization medication known to affect CYP1A2 activity, showed consistent results.

The LS means of CYP1A2 on Day 90 were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs spanning 100%.

11.2.5 Product Consumption During the Study

Subject listings of product usage are provided in [Appendix 15, Listing 15.3.2.1.1](#), [Listing 15.3.2.1.2](#), and [Listing 15.3.2.1.3](#).

No subjects in the PP Set used their allocated product outside the time windows pre-defined by the protocol.

Details of subjects' product consumption during the course of the study are presented in [Section 10.5](#) and [Section 10.6](#).



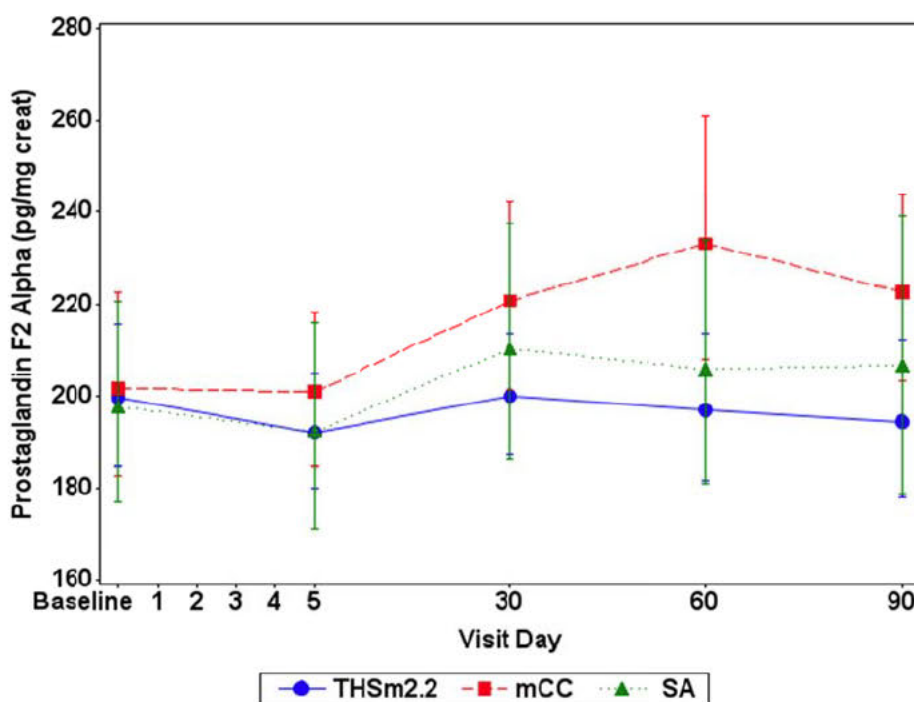
11.2.6 Analysis of Risk Markers During the Study

11.2.6.1 Risk Marker of Oxidative Stress: 8-epi-prostaglandine F_{2α} in 24-hour Urine (Concentration Adjusted for Creatinine) During the Study

Subject listings of 8-epi-PGF_{2α} data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of the urinary concentration of 8-epi-PGF_{2α} adjusted for creatinine during the course of the study are provided in [Appendix 15, Table 15.2.4.32.1](#) together with changes from baseline. The results for the PP Set are also presented graphically in [Figure 24](#) and in [Appendix 15, Figure 15.1.2.3.1](#). The results for the FAS are presented graphically in [Appendix 15, Figure 15.1.2.3.2](#).

Figure 24 Geometric Mean and 95% CI 8-epi-PGF_{2α} Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 8-epi-PGF_{2α} = prostaglandin F₂ alpha; CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).



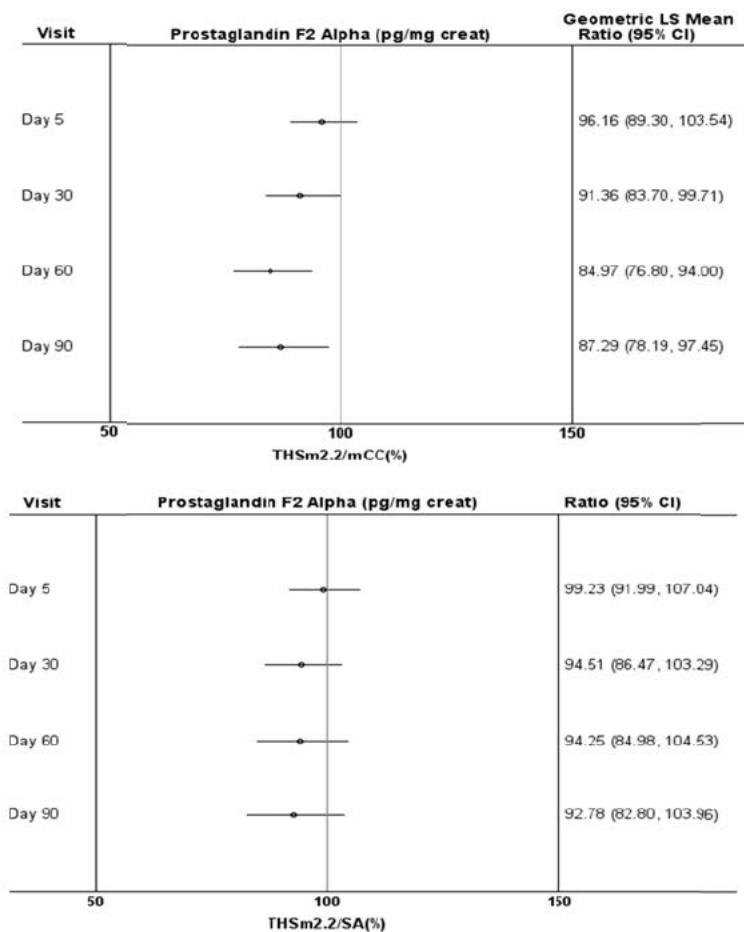
At baseline, the mean concentrations of 8-epi-PGF_{2α} adjusted for creatinine were 199.56, 201.65, and 197.64 pg/mg creat for the THS 2.2 Menthol, mCC, and SA arms respectively. On Day 5, the mean concentrations of 8-epi-PGF_{2α} adjusted for creatinine were 192.01, 200.83, and 192.23 pg/mg creat for the THS 2.2 Menthol, mCC, and SA arms, respectively.

During the Ambulatory Period, the mean 8-epi-PGF_{2α} values in the THS 2.2 Menthol arm were 199.96, 196.87, and 194.40 pg/mg creat for Days 30, 60, and 90, respectively. The mean 8-epi-PGF_{2α} values in the mCC arm were 220.64, 232.97, and 222.48 pg/mg creat and the mean 8-epi-PGF_{2α} values in the SA arm were 210.25, 205.75, and 206.59 pg/mg creat, for Days 30, 60, and 90, respectively.

Analyses of 8-epi-PGF_{2α} urinary concentration adjusted for creatinine for THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The analyses for the PP Set are also presented graphically in [Figure 25 \(Appendix 15, Figure 15.1.2.2\)](#), and tabulated in [Table 104](#) and [Table 105](#) for Days 5 and 90, respectively.



Figure 25 Forest Plot of Statistical Analysis of 8-epi-PGF_{2α} (pg/mg creat) During the Course of the Study (PP Set)



Abbreviations: 8-epi-PGF_{2α} = prostaglandin F₂ alpha; CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)

**Table 104 Analysis of 8-epi-PGF_{2α} versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC)		
				(%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS 2.2	76	192.24	96.16	19.63	89.30, 103.54
	mCC	42	199.92			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA)		
				(%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	192.24	99.23	19.63	91.99, 107.04
	SA	39	193.73			

Abbreviations: 8-epi-PGF_{2α} = prostaglandin F2 alpha; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#).

On Day 5, the LS means of 8-epi-PGF_{2α} concentration adjusted for creatinine were comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 100%.

On Day 5, there were no notable differences observed in the LS means of 8-epi-PGF_{2α} concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100%.

Analysis using the FAS showed consistent results to those presented.

**Table 105 Analysis of 8-epi-PGF_{2α} versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	193.56	87.29	28.86	78.19, 97.45
	mCC	41	221.74			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	193.56	92.78	28.86	82.80, 103.96
	SA	37	208.62			

Abbreviations: 8-epi-PGF_{2α} = prostaglandin F2 alpha; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#).

During the Ambulatory Period on Days 30, 60, and 90, the LS means of 8-epi-PGF_{2α} concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use were lower (8.64%, 15.03%, and 12.71%, respectively) than that observed in subjects who continued to smoke mCC, with 95% CIs excluding 100% at all time points ([Figure 25](#) and [Table 105](#)).

On Days 30, 60, and 90, there were no notable difference observed in the LS means of 8-epi-PGF_{2α} concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100% at all time points.

Analysis using the FAS showed consistent results to those presented.

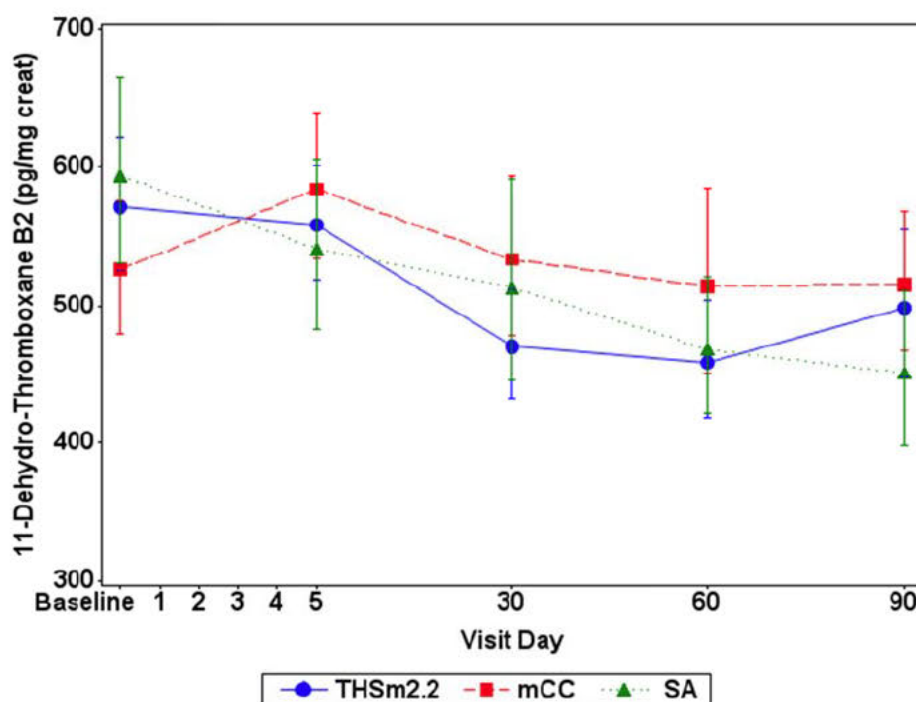
11.2.6.2 Risk Marker of Platelet Activation: 11-dehydrothromboxane B2 in 24-hour Urine (Concentration Adjusted for Creatinine) During the Study

Subject listings of 11-DTX-B2 data are provided in [Appendix 15, Listing 15.3.3.1](#).



Descriptive statistics of the urinary concentration of 11-DTX-B2 adjusted for creatinine at baseline and during the course of the study are provided in [Appendix 15, Table 15.2.4.32.1](#) together with changes from baseline. The results for the PP Set are also presented graphically in [Figure 26](#) and in [Appendix 15, Figure 15.1.2.3.1](#). The results for the FAS are presented graphically in [Appendix 15, Figure 15.1.2.3.2](#).

Figure 26 Geometric Mean and 95% CI 11-DTX-B2 Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THSm2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#)

At baseline, the mean concentrations of 11-DTX-B2 adjusted for creatinine were 571.09, 525.88, and 594.06 pg/mg creat, for the THSm2.2 Menthol, mCC, and SA arms respectively. On Day 5, the mean concentrations of 11-DTX-B2 adjusted for creatinine were 558.30, 584.24, and 540.80 pg/mg creat in the THSm2.2 Menthol, mCC, and SA arms, respectively.



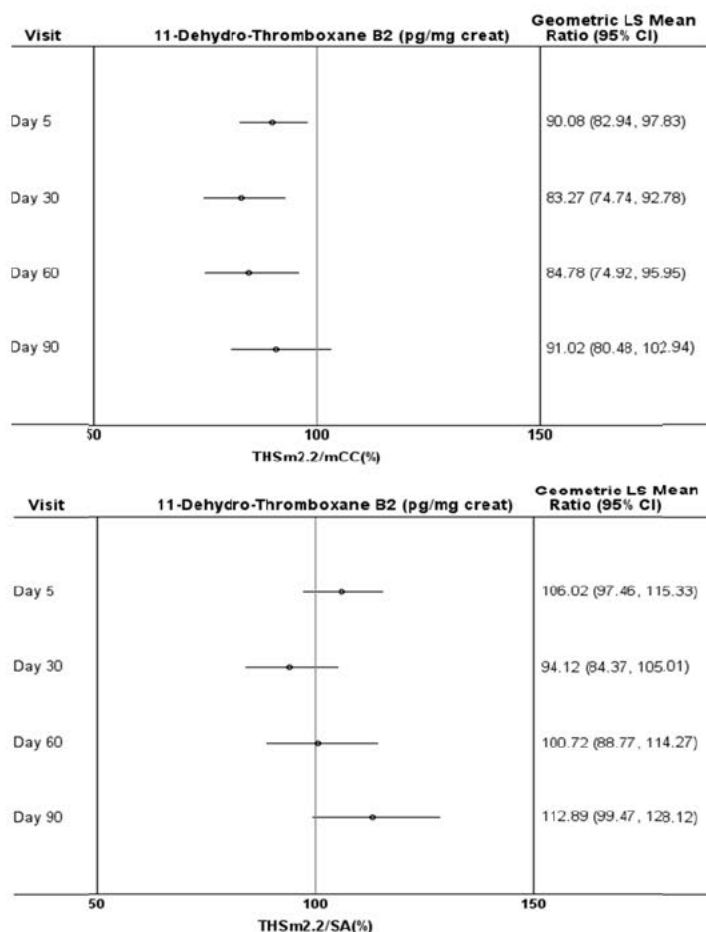
During the Ambulatory Period, the mean 11-DTX-B2 values in the THS 2.2 Menthol arm were 470.24, 458.84, and 498.22 pg/mg creat for Days 30, 60, and 90, respectively. The mean 11-DTX-B2 values in the mCC arm were 533.11, 513.62, and 515.18 pg/mg creat and the mean 11-DTX-B2 values in the SA arm were 513.17, 468.25, and 450.76 pg/mg creat, for Days 30, 60, and 90, respectively.

In addition, descriptive statistics and statistical analyses of 11-DTX-B2 excluding assessments within 5 half-lives of a concomitant medication known to affect the production of 11-DTX-B2 are tabulated in [Appendix 15, Table 15.2.4.25.1.1](#) and [Table 15.2.4.32.2.1](#) for the PP Set and FAS, respectively. However, as no assessments were excluded as no concomitant medication that would impact 11-DTX-B2 was recorded in the study, this data are only provided in the appendices.

Analyses of 11-DTX-B2 urinary concentration adjusted for creatinine for THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The analyses for the PP Set are also presented graphically in [Figure 27 \(Appendix 15, Figure 15.1.2.2\)](#), and tabulated in [Table 106](#) and [Table 107](#) for Days 5 and 90, respectively.



Figure 27 Forest Plot of Statistical Analysis of 11-DTX-B2 (pg/mg creat) During the Course of the Study (PP Set)



Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; TBS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)

**Table 106 Analysis of 11-DTX-B2 versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC)		
				(%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	557.12	90.08	21.86	82.94, 97.83
	mCC	42	618.47			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA)		
				(%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	557.12	106.02	21.86	97.46, 115.33
	SA	39	525.50			

Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; mCC = Menthol conventional cigarette; PP = per protocol; LS = least squares; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#)

On Day 5, the LS mean of 11-DTX-B2 concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 9.92% lower than that of subjects who continued to smoke mCC (95% CI: 2.17, 17.06).

On Day 5, there were no notable differences observed in the LS means of 11-DTX-B2 concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs spanning 100%.

Analysis using the FAS showed consistent results to those presented.

**Table 107 Analysis of 11-DTX-B2 versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC)		
				(%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	500.52	91.02	32.24	80.48, 102.94
	mCC	41	549.90			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA)		
				(%)	CV%	95% CI
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	500.52	112.89	32.24	99.47, 128.12
	SA	37	443.37			

Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; mCC = Menthol conventional cigarette; PP = per protocol; LS = least squares; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#)

During the Ambulatory Period on Days 30 and 60, the LS means of 11-DTX-B2 concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use were 16.73% and 15.22% lower, respectively, than that observed in subjects who continued to smoke mCC, with 95% CI excluding 100% ([Figure 27](#)). On Day 90, the LS mean of 11-DTX-B2 concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 8.98% lower than that observed in subjects who continued to smoke mCC (95% CI: -2.94, 19.52).

On Days 30 and 60, there was no notable difference observed in the LS means of 11-DTX-B2 concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%. On Day 90, the LS mean of 11-DTX-B2 concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 12.89% higher than that observed in subjects who abstained from smoking (95% CI: -0.53, 28.12).

Analysis using the FAS showed consistent results to those presented.

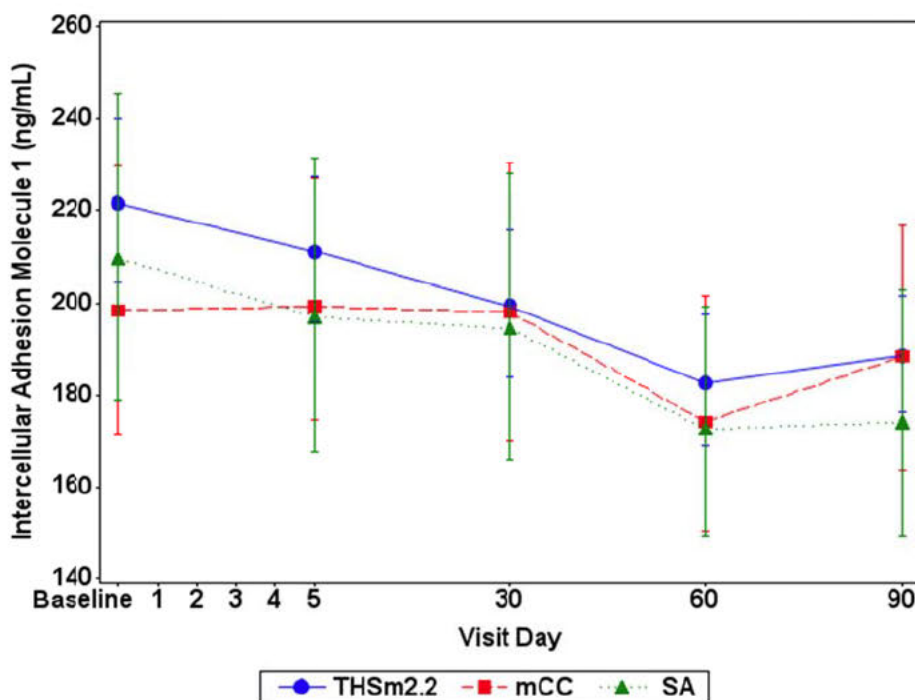


11.2.6.3 Risk Marker of Endothelial Dysfunction: sICAM-1 in Serum During the Study

Subject listings of sICAM-1 data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of sICAM-1 collected during the study are provided in [Appendix 15, Table 15.2.4.30.1](#) and [Table 15.2.4.30.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results for the PP Set are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#), and in [Figure 28](#). The results for the FAS are presented graphically in [Appendix 15, Figure 15.1.2.3.2](#).

Figure 28 Geometric Mean and 95% CIs sICAM-1 (ng/mL) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; sICAM-1 = soluble intercellular adhesion molecule-1; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

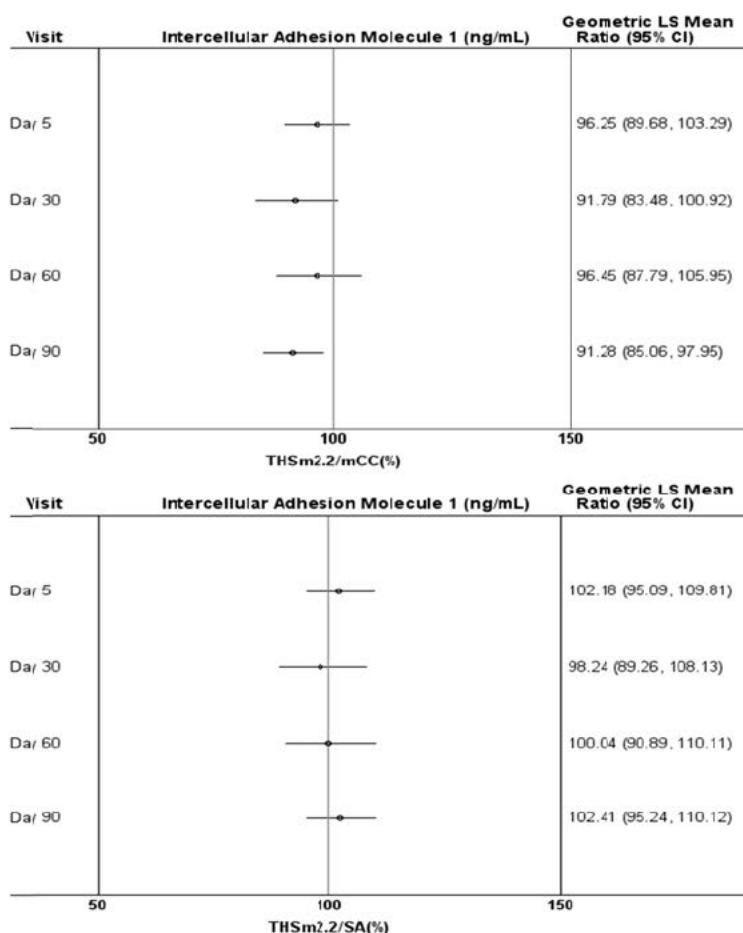
At baseline, the mean concentrations of sICAM-1 were 221.58, 198.41, and 209.54 ng/mL for the THS 2.2 Menthol, mCC, and SA arm, respectively. On Day of Discharge from the Confinement Period, the mean values of sICAM-1 were 211.00, 199.22, and 197.00 ng/mL for the THS 2.2 Menthol, mCC, and SA arms, respectively.



During the Ambulatory period, the mean sICAM-1 values in the THS 2.2 Menthol arm were 199.34, 182.66, and 188.43 ng/mL for Days 30, 60, and 90, respectively. The mean sICAM-1 values in the mCC arm were 197.99, 174.14, and 188.40 ng/mL and the mean sICAM-1 values in the SA arm were 194.43, 172.54, and 174.07 ng/mL, for Days 30, 60, and 90, respectively.

Analyses of sICAM-1 for THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.1](#) for the PP Set and FAS, respectively, and are also graphically presented in [Appendix 15, Figure 15.1.2.2](#). The statistical analyses for the PP Set are also presented in [Figure 29](#), and tabulated in [Table 108](#) and [Table 109](#) for Days 5 and 90, respectively.

Figure 29 Forest Plot of Statistical Analysis of sICAM-1 (ng/mL) During the Course of the Study (PP Set)





Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; sICAM-1 = soluble intercellular adhesion molecule-1; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)

Table 108 Analysis of sICAM-1 versus mCC and SA on Day of Discharge (Confinement Period) (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)		
				CV%	95% CI	
Concentration (ng/mL)	THS m2.2	76	204.22	96.25	18.62	89.68, 103.29
	mCC	42	212.19			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)		
				CV%	95% CI	
Concentration (ng/mL)	THS m2.2	76	204.22	102.18	18.62	95.09, 109.81
	SA	39	199.86			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; sICAM-1 = soluble intercellular adhesion molecule-1; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#)

On the Day of Discharge (Confinement), there were no notable differences between the LS means of sICAM-1 in subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 100%.

On the Day of Discharge (Confinement), the LS means of sICAM-1 were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100%.

Analysis using the FAS showed consistent results to those presented.

**Table 109 Analysis of sICAM-1 versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC)		
				(%)	CV%	95% CI
Concentration (ng/mL)	THS m2.2	70	181.23	91.28	18.16	85.06, 97.95
	mCC	41	198.55			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA)		
				(%)	CV%	95% CI
Concentration (ng/mL)	THS m2.2	70	181.23	102.41	18.16	95.24, 110.12
	SA	37	176.97			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; sICAM-1 = soluble intercellular adhesion molecule-1; THS m2.2 = Tobacco Heating System 2.2 Menthol. Adjusted geometric LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#)

During the Ambulatory Period, on Day 30, the LS mean of sICAM-1 in subjects who switched to THS 2.2 Menthol use was 8.21% lower than that observed in subjects who continued to smoke mCC (95% CI: 83.48, 100.92). On Day 60, there was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who continued smoking mCC. On Day 90, the LS mean of sICAM-1 in subjects who switched to THS 2.2 Menthol use was 8.72% lower than that observed in subjects who continued to smoke mCC (95% CI: 2.05, 14.94).

On Days 30, 60, and 90, there were no notable difference in the LS means of sICAM-1 between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs spanning 100% at all time points.

Analysis using the FAS showed consistent results to those presented.

11.2.6.4 Risk Markers of Lipid Metabolism: LDL Cholesterol, HDL Cholesterol, Triglycerides, and Total Cholesterol in Serum During the Study

Subject listings of TG, HDL cholesterol, LDL cholesterol, and TC in serum data are provided in [Appendix 15, Listing 15.3.3.2](#).

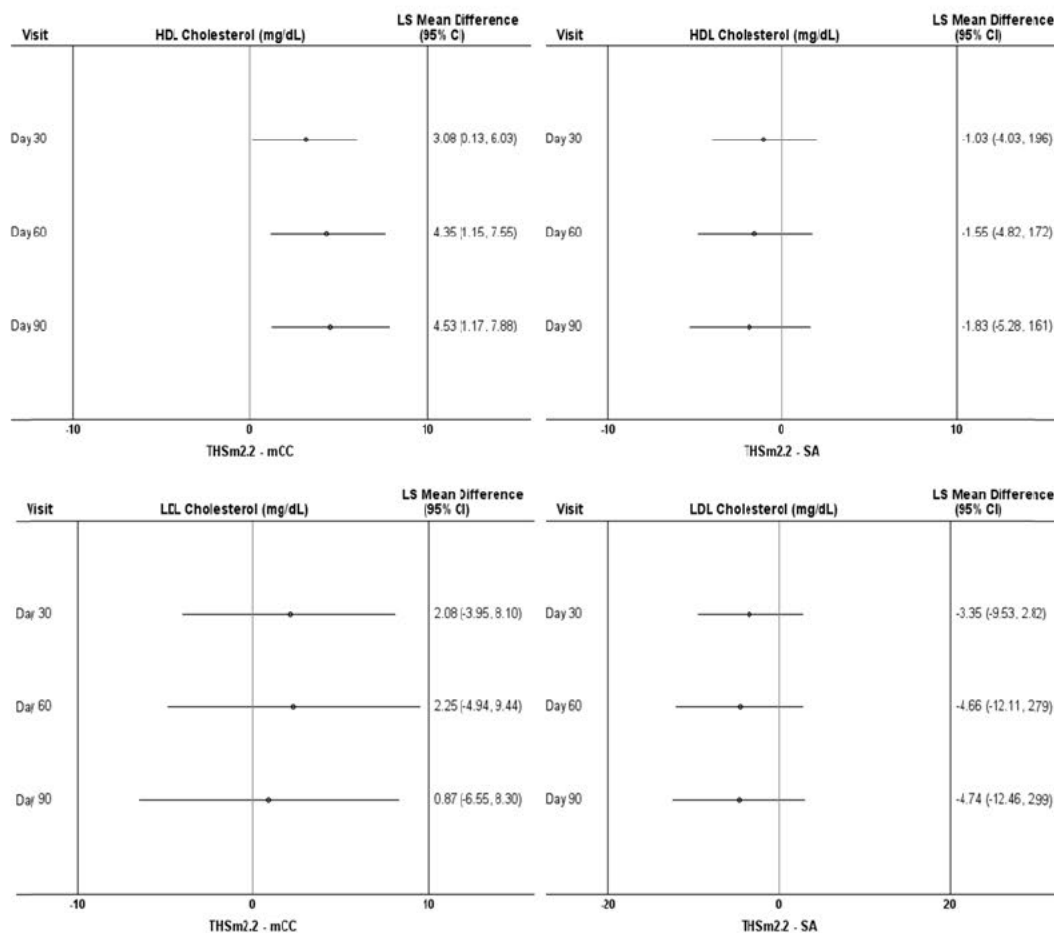


Descriptive statistics of HDL cholesterol, LDL cholesterol, TG, and TC in serum data during the course of the study are provided in [Appendix 15, Table 15.2.4.27.1](#) and [Table 15.2.4.27.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#) and [Figure 15.1.2.3.2](#) for the PP Set and FAS, respectively.

Analyses of HDL cholesterol, LDL cholesterol, TG, and TC for THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The statistical analyses for the PP Set are also presented graphically in [Appendix 15, Figure 15.1.2.2](#) and in [Figure 30](#) (HDL and LDL cholesterol) and [Figure 31](#) (TGs and TC).



Figure 30 Forest Plot of Statistical Analysis of HDL and LDL Cholesterol (mg/dL) During the Study (PP Set)

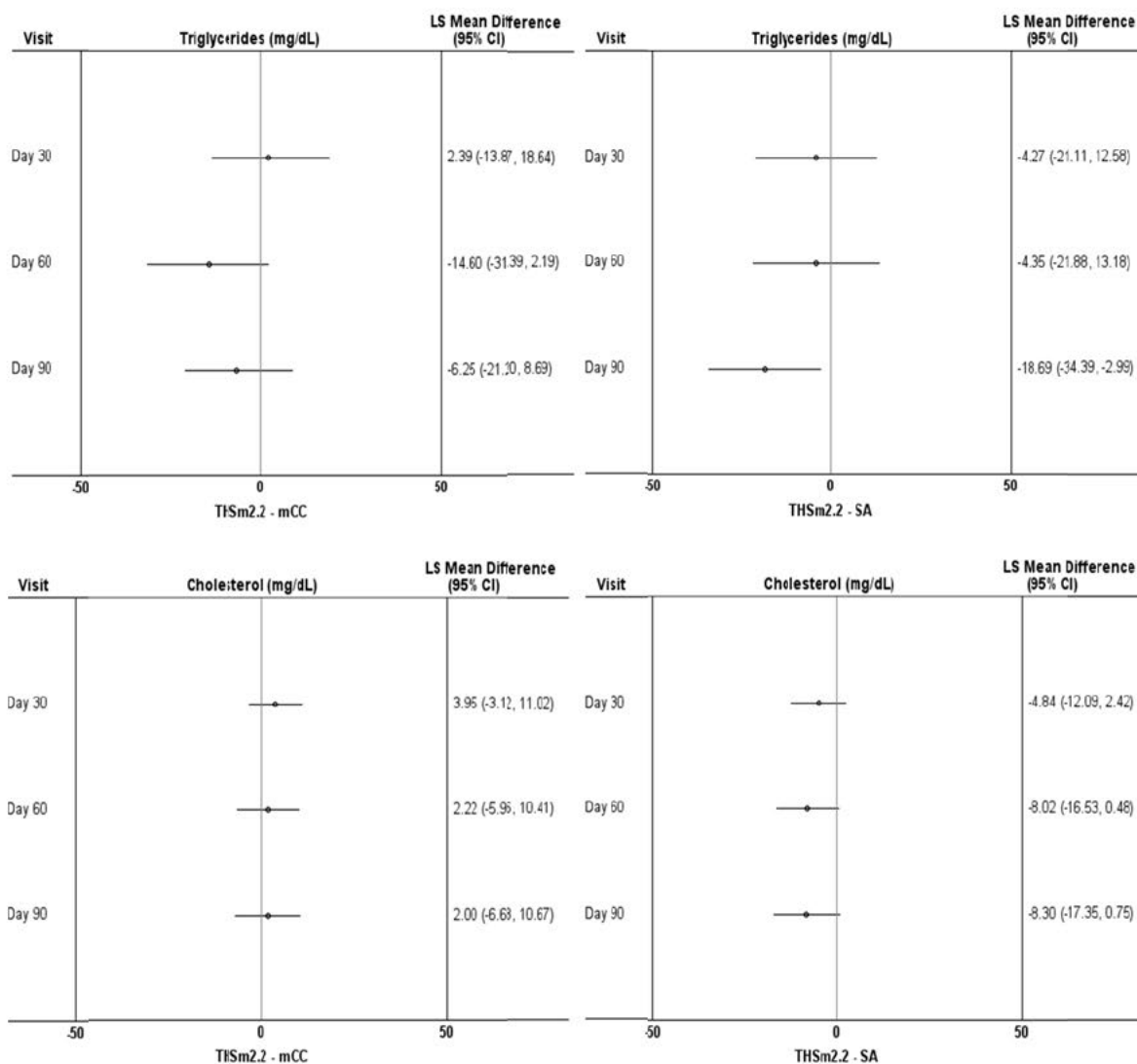


Abbreviations: CI = confidence intervals; HDL = high density lipoprotein; LDL = low density lipoprotein; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2](#)



Figure 31 Forest Plot of Statistical Analysis of Triglycerides (mg/dL) and Total Cholesterol (mg/dL) During the Study (PP Set)



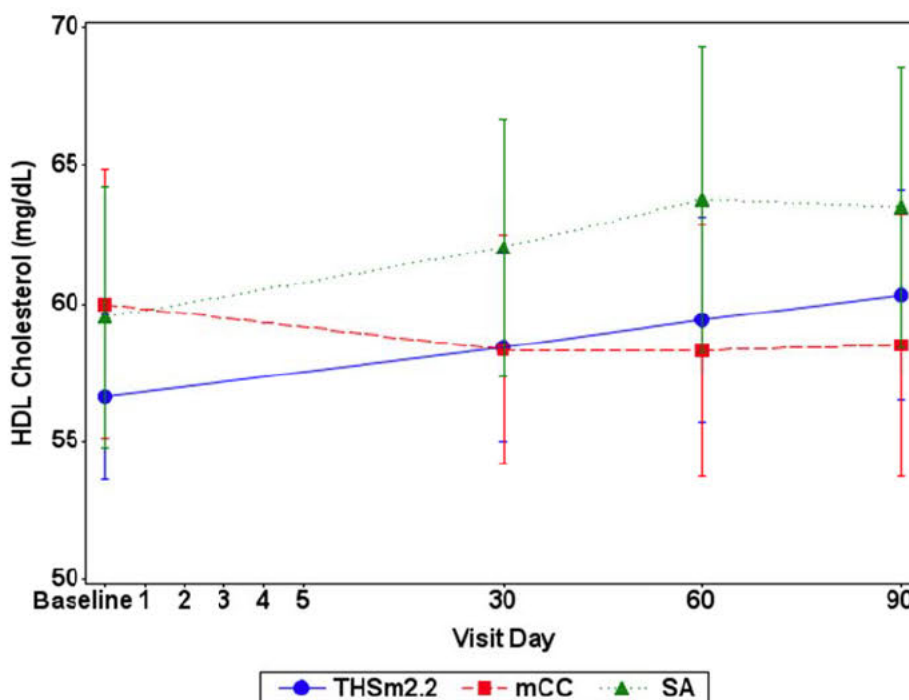
Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Figure 15.1.2.2](#)



11.2.6.4.1 HDL Cholesterol (mg/dL) During the Study

Data for HDL cholesterol for the PP Set are presented in [Figure 32](#).

Figure 32 Arithmetic Mean and 95% CI HDL Cholesterol (mg/dL) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; HDL = high density lipoprotein; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1.
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline (PP Set Period 2), the mean concentrations for HDL cholesterol were 56.5, 60.0, and 59.5 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean concentrations for HDL cholesterol were 58.4, 58.3, and 62.0 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean concentrations for HDL cholesterol were 59.4, 58.3, and 63.8 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 90, the mean concentrations for HDL cholesterol were 60.3, 58.5, and 63.5 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively.

On Days 30, 60, and 90, the LS means of HDL cholesterol in subjects who switched to THS 2.2 Menthol use were higher (3.08, 4.35, and 4.53 mg/dL, respectively) than that



observed in subjects who continued to smoke mCC, with 95% CIs excluding 0 at all time points (Figure 30).

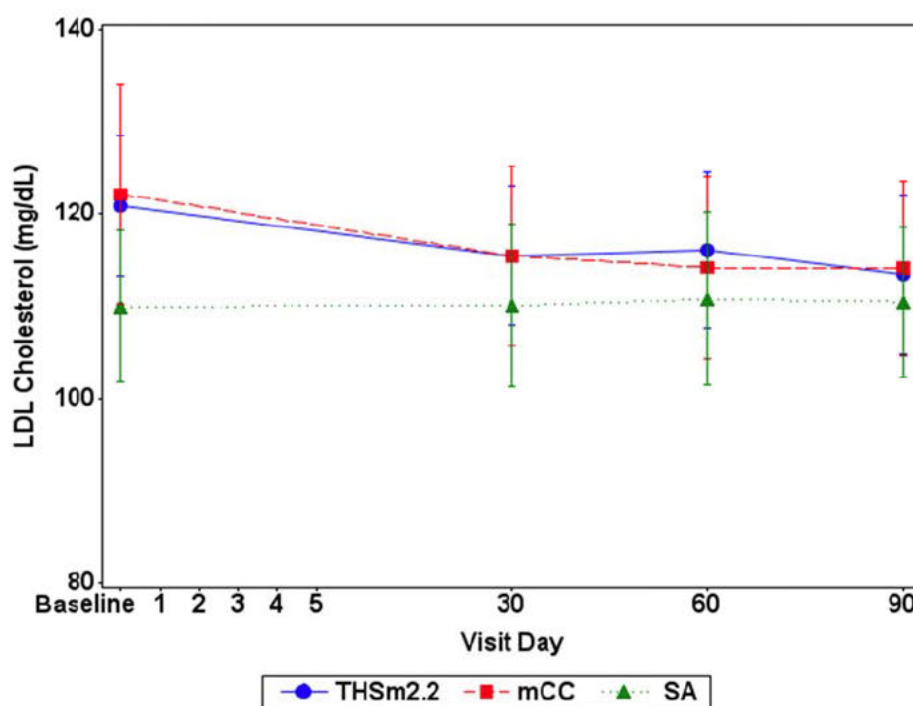
On Days 30, 60, and 90, there were no notable differences observed in the LS means of HDL cholesterol between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points (Figure 30).

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.4.2 LDL Cholesterol (mg/dL) During the Study

Data for LDL cholesterol for the PP Set are presented in Figure 33.

Figure 33 Arithmetic Mean and 95% CI LDL Cholesterol (mg/dL) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; LDL = low density lipoprotein; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1. Data Source: Appendix 15, Figure 15.1.2.3.1.



At baseline (PP Set Period 2), the mean concentrations for LDL cholesterol were 120.8, 123.3, and 110.0 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean concentrations for LDL cholesterol were 115.4, 115.4, and 110.1 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean concentrations for LDL cholesterol were 116.0, 114.1, and 110.8 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 90, the mean concentrations for LDL cholesterol were 113.4, 114.1, and 110.5 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively.

On Days 30, 60, and 90, there were no notable differences observed in the LS means of LDL cholesterol between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 0 at all time points ([Figure 30](#)).

On Days 30, 60, and 90, there were no notable difference observed in the LS means of LDL cholesterol between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points ([Figure 30](#)).

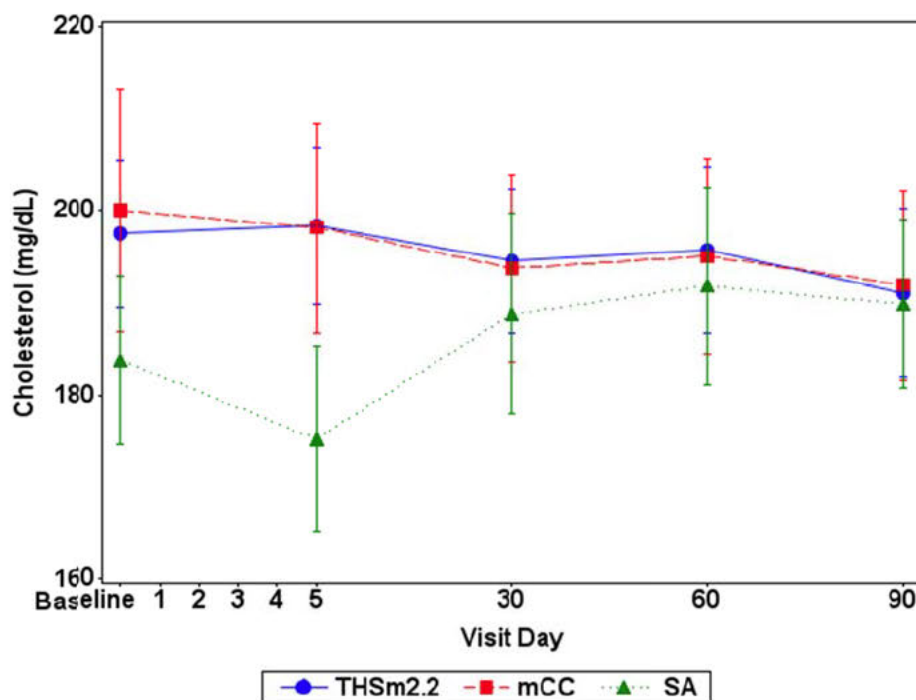
Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.4.3 Total Cholesterol (mg/dL) During the Study

Data for TC for the PP Set are presented in [Figure 34](#).



Figure 34 Arithmetic Mean and 95% CI Total Cholesterol (mg/dL) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline (PP Set Period 1), the mean concentrations for TC were 197.5, 200.1, and 183.8 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean concentrations for TC were 194.6, 193.8, and 188.8 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean concentrations for TC were 195.7, 195.1, and 191.9 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day of Discharge from the Ambulatory Period, the mean concentrations for TC were 191.1, 192.0, and 189.9 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively.

On Days 30, 60, and Day of Discharge, there were no notable differences observed in the LS means of TC between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 0 at all time points ([Figure 31](#)).



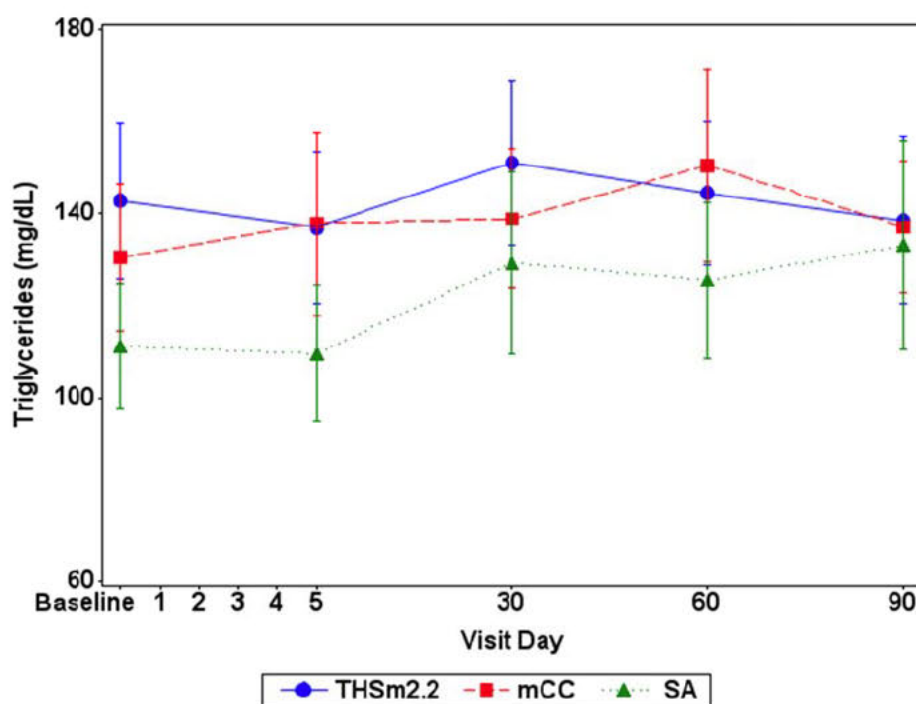
On Days 30, 60, and Day of Discharge, there were no notable differences observed in the LS means of TC between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points (Figure 31).

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.4.4 Triglycerides (mg/dL) During the Study

Data for TGs for the PP Set are presented in Figure 35.

Figure 35 Arithmetic Mean and 95% CI Triglycerides (mg/dL) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 00:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1. Data Source: Appendix 15, Figure 15.1.2.3.1.

At baseline, the mean concentrations for TGs were 142.8, 130.5, and 111.3 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean concentrations for TGs were 151.0, 138.9, and 120.3 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean concentrations for TGs were 144.5, 150.5, and



125.6 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day of Discharge from the Ambulatory Period, the mean concentrations for TGs were 138.5, 137.2, and 133.1 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively.

On Day 30 and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of TGs between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 0. On Day 60, the LS mean of TGs in subjects who switched to THS 2.2 Menthol use was 14.60 mg/dL lower than subjects who continued to smoke mCC (95% CI: -31.39, 2.19; [Figure 31](#)).

On Days 30 and 60, there were no notable differences observed in the LS means of TGs between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0. On the Day of Discharge (Ambulatory), the LS mean of TGs in subjects who switched to THS 2.2 Menthol use was 18.69 mg/dL lower than in subjects who abstained from smoking (95% CI: -34.39, -2.99; [Figure 31](#)).

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.5 Risk Markers of Inflammation: Platelet Count and WBC Total and Differential Counts in Blood During the Study

Subject listings of platelet data and WBC Total and differential counts are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of platelet data and WBC Total and differential counts during the study are provided in [Appendix 15, Table 15.2.4.31.1](#) and [Table 15.2.4.31.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#) and [Figure 15.1.2.3.2](#) for the PP Set and FAS, respectively.

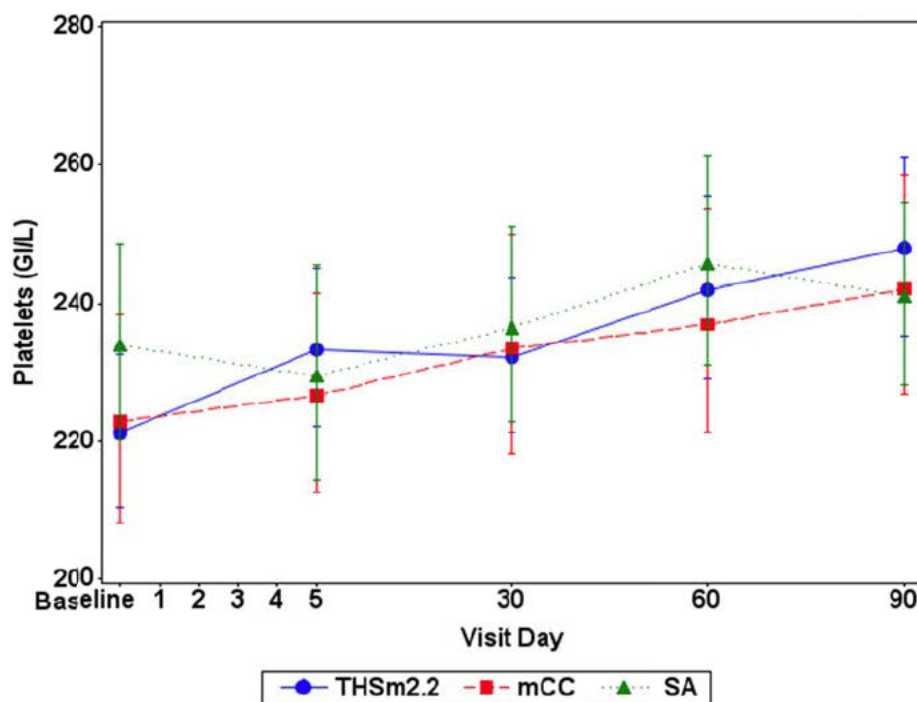
Analyses of platelets and WBC differential counts for THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The statistical analyses are also presented graphically in [Appendix 15, Figure 15.1.2.2](#).

11.2.6.5.1 Platelet Count (GI/L) During the Study

Data for platelet count for the PP Set are presented in [Figure 36](#).



Figure 36 Geometric Mean and 95% CI Platelets (G/L) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

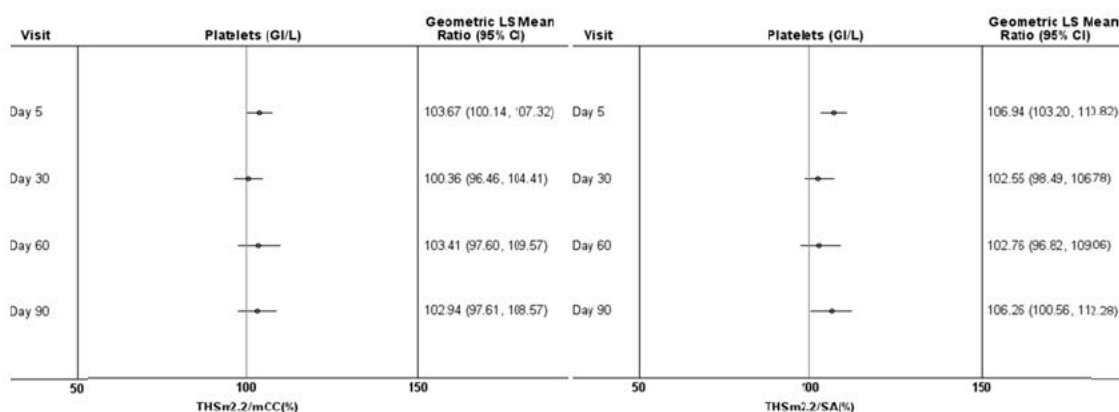
Data Source: [Appendix 15, Figure 15.1.2.3.1.](#)



At baseline, the mean platelet counts were 221.2, 222.9, and 233.9 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Confinement Period, the mean platelet counts were 233.3, 226.6, and 229.4 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean platelet counts were 232.2, 233.5, and 236.5 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean platelet counts were 241.9, 236.9, and 245.7 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean platelet counts were 247.9, 242.1, and 241.0 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of platelet counts for the PP Set are presented in [Figure 37](#).

Figure 37 Forest Plot of Statistical Analysis of Platelet Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Day 5, the LS mean of platelet counts in subjects who switched to THS 2.2 Menthol use was 3.67% higher than that observed in subject who continued to smoke mCC, with 95 % CI excluding 100% (95% CI: 100.14, 107.32).

On Days 30 and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of platelet counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 100% at all time points.



On Day 5, the LS mean of platelet counts in subjects who switched to THS 2.2 Menthol use was 6.94% higher than that observed in subject who abstained from smoking, with 95 % CI excluding 100% (95% CI: 103.20, 110.32).

On Days 30 and 60, there were no notable differences observed in the LS means of platelet counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95 % CI spanning 100% at all time points.

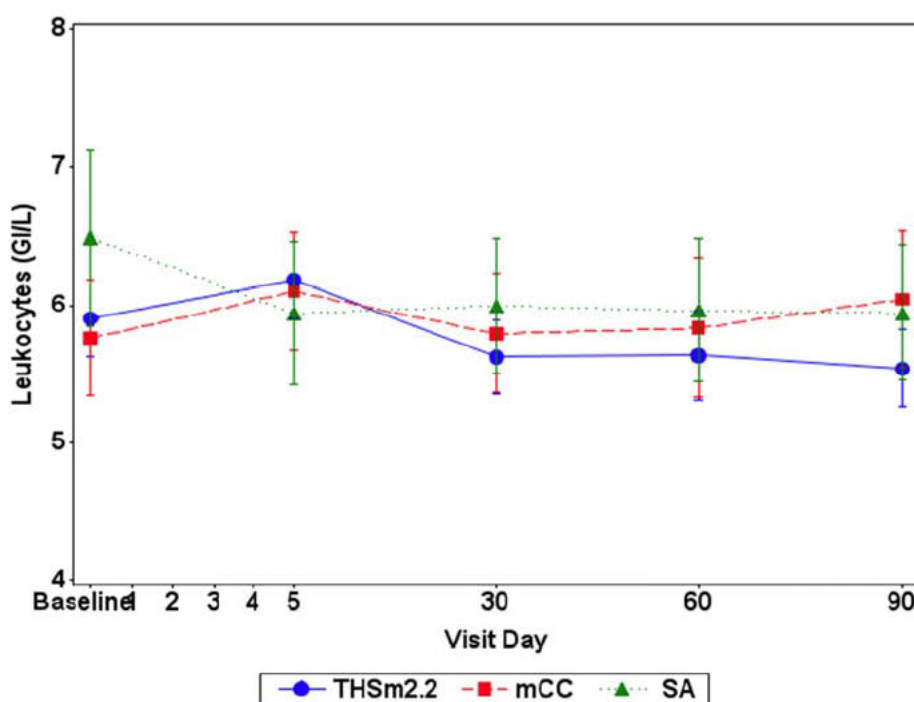
On the Day of Discharge (Ambulatory), the LS mean of platelet counts in subjects who switched to THS 2.2 Menthol use was 6.26% higher than that observed in subject who abstained from smoking, with 95% CI excluding 100% (95% CI: 100.56, 112.28).

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95 % CI around 0.

11.2.6.5.2 Total White Blood Cell (leukocytes) Count (G/L) During the Study

Data for total WBC count (leukocyte count) for the PP Set are presented in [Figure 38](#).

Figure 38 Arithmetic Mean and 95% CI Leukocytes (G/L) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.



Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

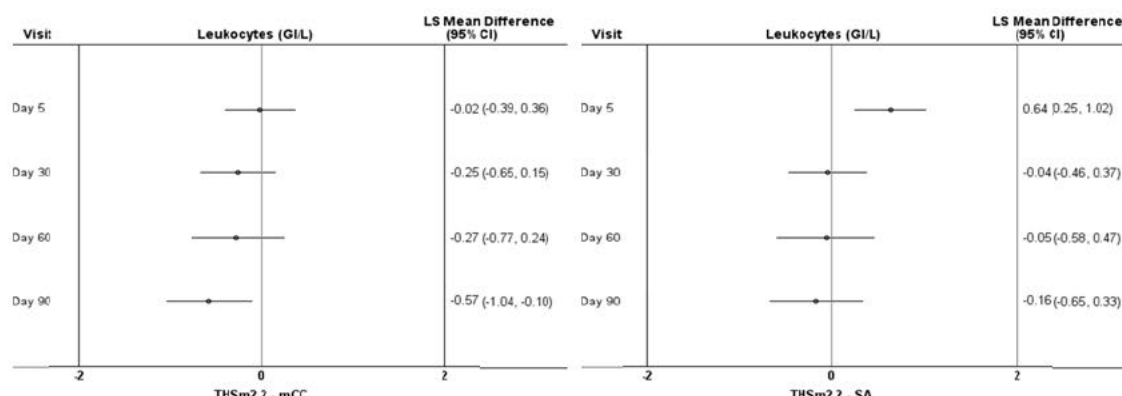
Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, the mean leukocyte counts were 5.905, 5.763, and 6.483 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from Confinement Period, the mean leukocyte counts were 6.184, 6.101, and 5.942 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean leukocyte counts were 5.625, 5.796, and 5.996 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean leukocyte counts were 5.635, 5.837, and 5.961 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean leukocyte counts were 5.533, 6.044, and 5.943 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of leukocyte counts for the PP Set are presented in [Figure 39](#).

Figure 39 Forest Plot of Statistical Analysis of Leukocyte Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 5, 30, and 60, there were no notable differences observed in the LS means of leukocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0 at all time points.

On the Day of Discharge (Ambulatory), the LS mean of leukocyte counts in subjects who switched to THS 2.2 Menthol use was 0.57 GI/L lower than that observed in subject who continued to smoke mCC, with 95% CI excluding 0 (95% CI: -1.04, -0.10).



On Day 5, the LS mean of leukocyte counts in subjects who switched to THS 2.2 Menthol use was 0.64 GI/L higher than that observed in subject who abstained from smoking, with 95 % CI excluding 0 (95% CI: 0.25, 1.02).

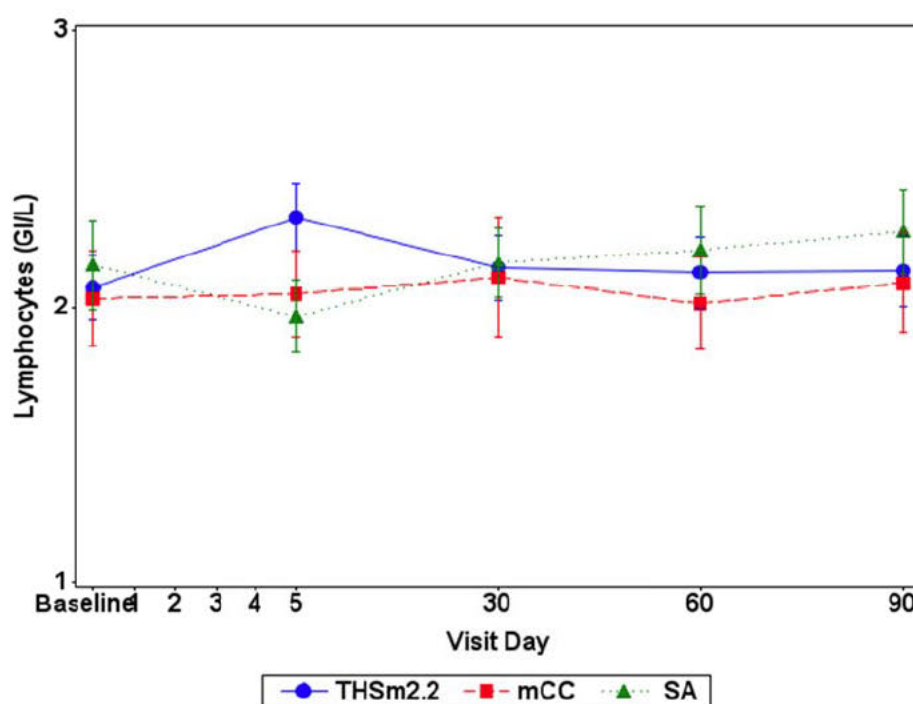
On Days 30 and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of leukocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with 95% CIs spanning 0 at all time points.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95 % CI around 0.

11.2.6.5.3 Lymphocyte Count (GI/L) During the Study

Data for lymphocyte count for the PP Set are presented in [Figure 40](#).

Figure 40 Arithmetic Mean and 95% CI Lymphocytes (GI/L) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

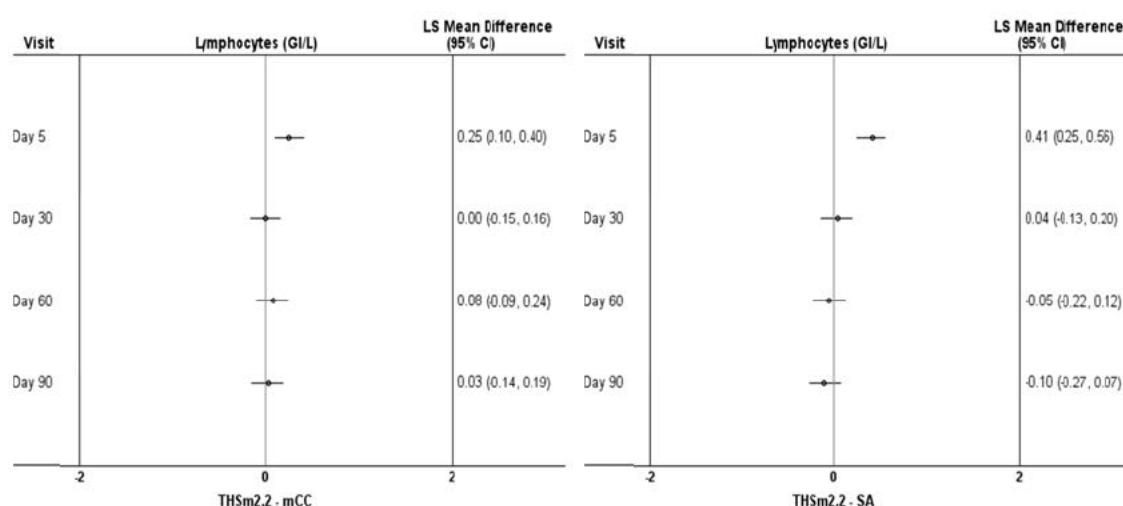
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).



At baseline, the mean lymphocyte counts were 2.065, 2.026, and 2.147 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge (Confinement), the mean lymphocyte counts were 2.319, 2.042, and 1.961 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean lymphocyte counts were 2.135, 2.101, and 2.154 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean lymphocyte counts were 2.119, 2.109, and 2.199 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean lymphocyte counts were 2.123, 2.082, and 2.258 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of lymphocyte counts for the PP Set are presented in [Figure 41](#).

Figure 41 Forest Plot of Statistical Analysis of Lymphocyte Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Day 5, the LS mean of lymphocyte counts in subjects who switched to THS 2.2 Menthol use was 0.25 GI/L higher than that observed in subject who continued to smoke mCC, with 95% CI excluding 0 (95% CI: 0.10, 0.40).

On Days 30 and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of lymphocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0 at all time points.



On Day 5, the LS mean of lymphocyte counts in subjects who switched to THS 2.2 Menthol use was 0.41 $\times 10^9/L$ higher than that observed in subject who abstained from smoking, with 95% CI excluding 0 (95% CI: 0.05, 0.56).

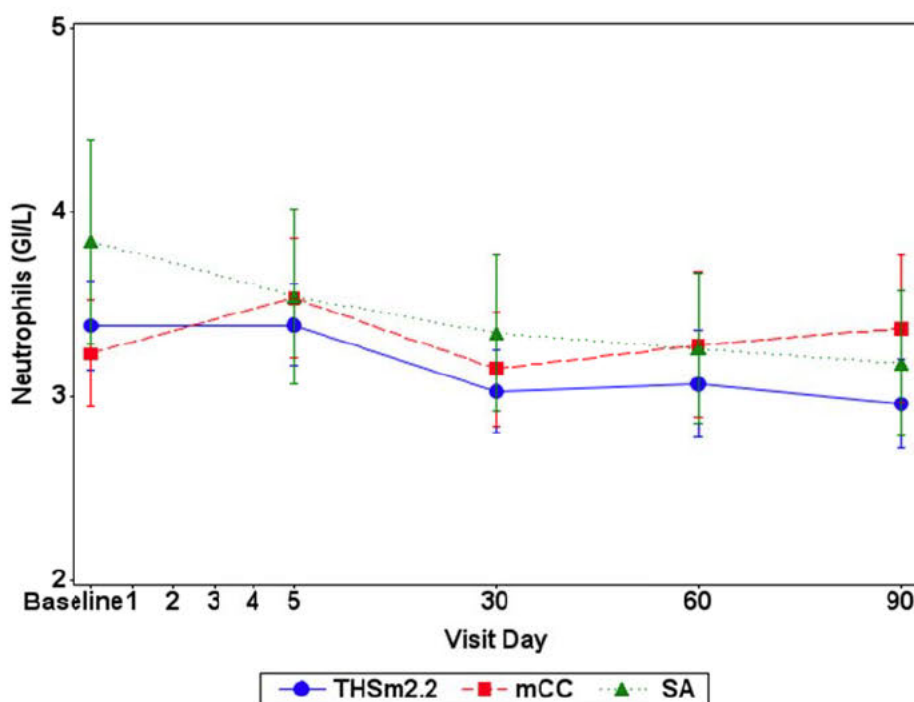
On Days 30 and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of lymphocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.5.4 Neutrophil Count (G/L) During the Study

Data for neutrophil count for the PP Set are presented in [Figure 42](#).

Figure 42 Arithmetic Mean and 95% CI Neutrophils (G/L) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

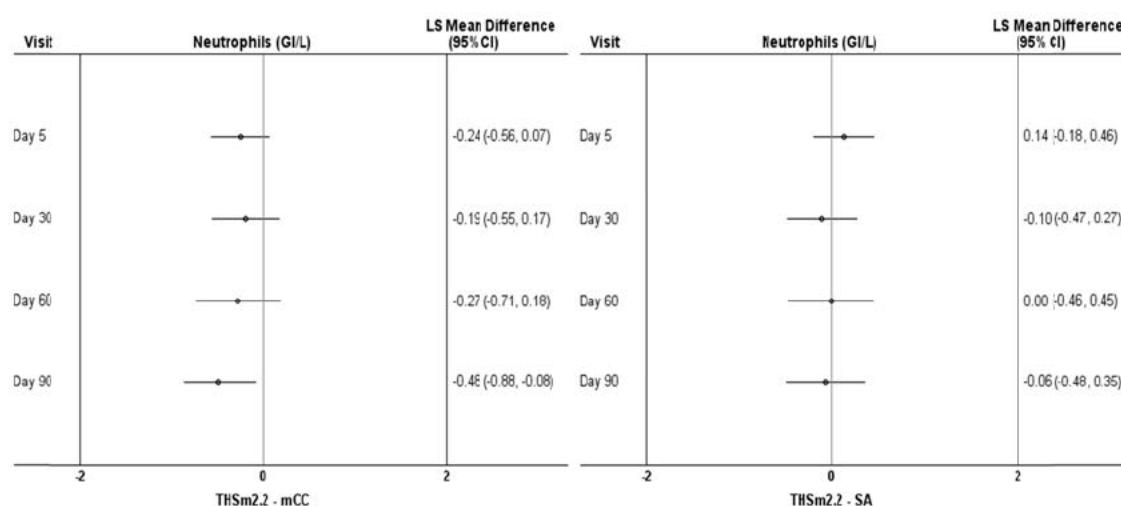
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).



At baseline, the mean neutrophil counts were 3.380, 3.226, and 3.838 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from Confinement Period, the mean neutrophil counts were 3.383, 3.531, and 3.541 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean neutrophil counts were 3.024, 3.146, and 3.340 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean neutrophil counts were 3.063, 3.273, and 3.253 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean neutrophil counts were 2.954, 3.366, and 3.175 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of neutrophil counts for the PP Set are presented in Figure 43.

Figure 43 Forest Plot of Statistical Analysis of Neutrophil Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 5, 30, and 60, there were no notable differences observed in the LS means of neutrophil counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0 at all time points.

On the Day of Discharge (Ambulatory), the LS mean of neutrophil counts in subjects who switched to THS 2.2 Menthol use was 0.48 GI/L lower than that observed in subject who continued to smoke mCC, with 95% CI excluding 0 (95% CI: -0.88, -0.08).

On Days 5, 30, and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of neutrophil counts between subjects who



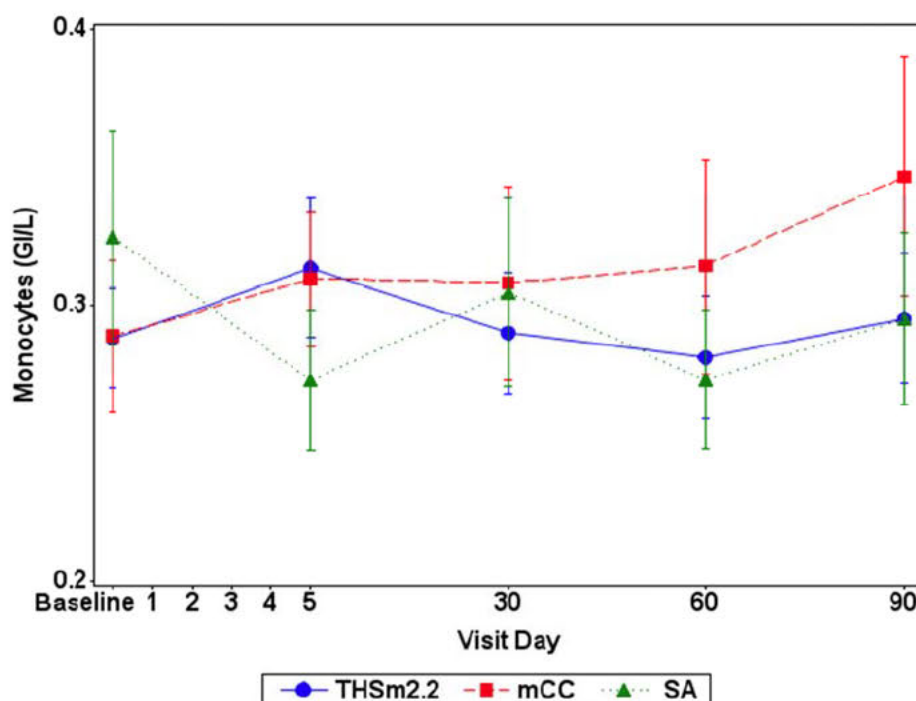
switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95 % CI spanning 0 at all time points.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95 % CI around 0.

11.2.6.5.5 Monocyte Count (GI/L) During the Study

Data for monocyte count for the PP Set are presented in [Figure 44](#).

Figure 44 Arithmetic Mean and 95% CI Monocytes (GI/L) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.
Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.
Baseline is summarized using the baseline data from the PP Set for Period 1.
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

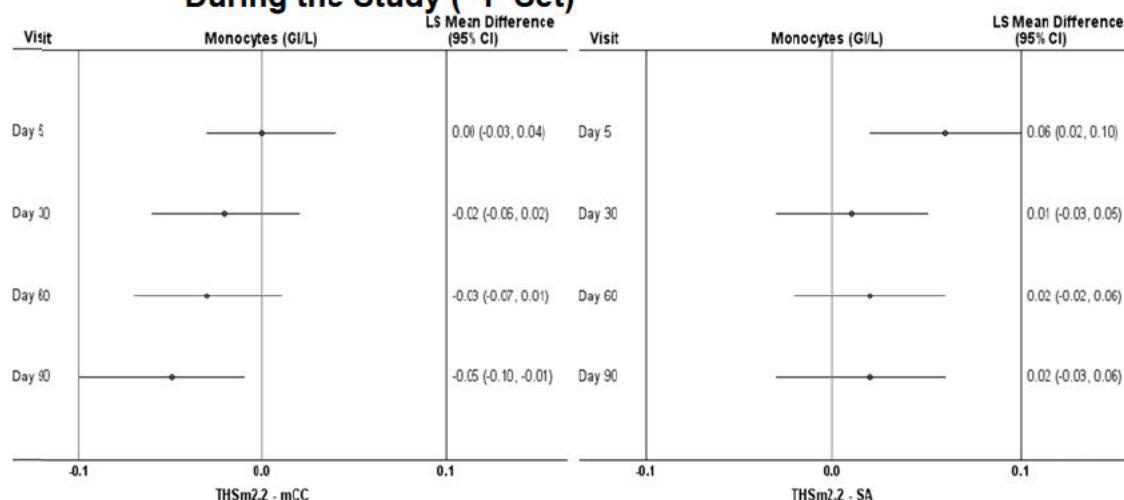
At baseline, the mean monocyte counts were 0.288, 0.289, and 0.324 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from Confinement Period, the mean monocyte counts were 0.313, 0.309, and 0.273 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean monocyte counts were 0.290, 0.308, and 0.304 GI/L for the THS 2.2 Menthol, mCC, and SA arms,



respectively. On Day 60, the mean monocyte counts were 0.281, 0.314, and 0.273 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean monocyte counts were 0.293, 0.347, and 0.295 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of monocyte counts for the PP Set are presented in [Figure 45](#).

Figure 45 Forest Plot of Statistical Analysis of Monocyte Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 5, 30, and 60, there were no notable differences observed in the LS means of monocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0 at all time points.

On the Day of Discharge (Ambulatory), the LS mean of monocyte counts in subjects who switched to THS 2.2 Menthol use was 0.05 GI/L lower than that observed in subject who continued to smoke mCC, with 95% CI excluding 0 (95% CI: -0.10, -0.01).

On Day 5, the LS mean of monocyte counts in subjects who switched to THS 2.2 Menthol use was 0.06 higher than that observed in subject who abstained from smoking, with 95% CI excluding 0 (95% CI: 0.02, 0.10).

On Days 30 and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of monocyte counts between subjects who switched

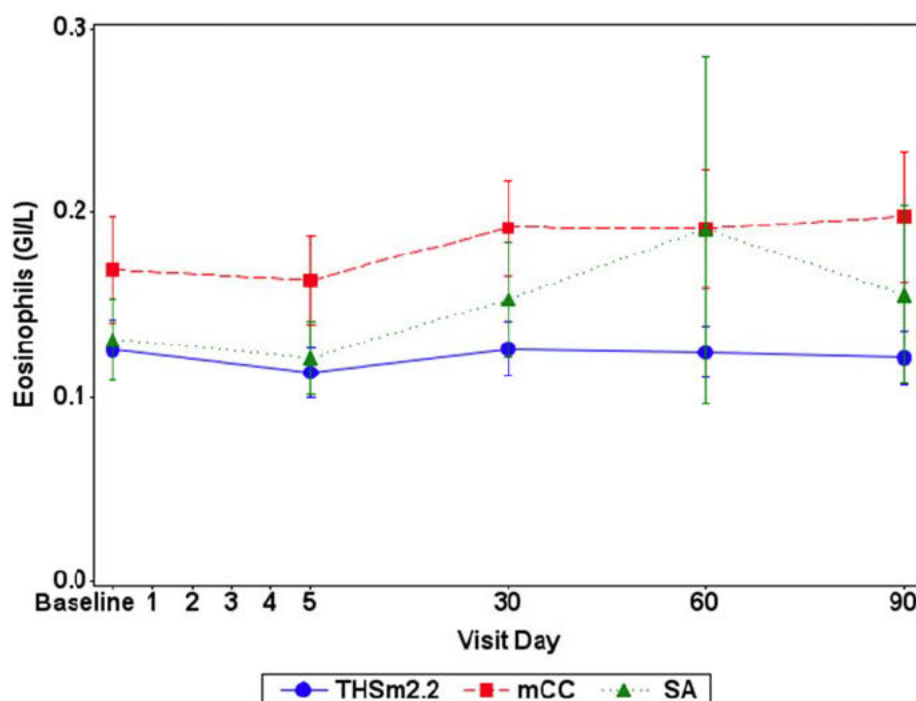
to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.5.6 Eosinophil Count (GI/L) During the Study

Data for eosinophil count for the PP Set are presented in [Figure 46](#).

Figure 46 Arithmetic Mean and 95% CI Eosinophils (GI/L) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

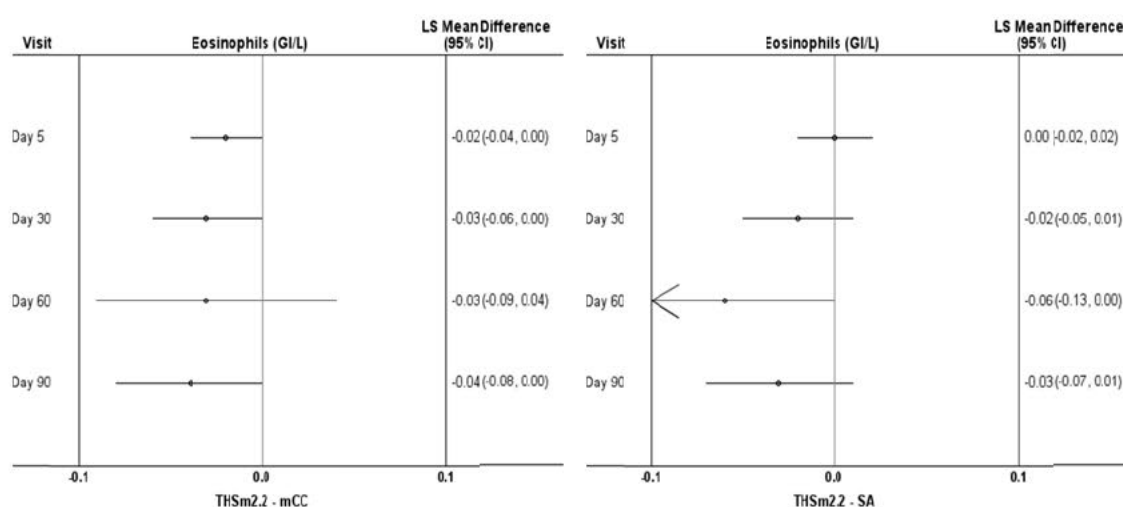
At baseline, the mean eosinophil counts were 0.125, 0.163, and 0.131 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from Confinement Period, the mean eosinophil counts were 0.113, 0.163, and 0.121 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean eosinophil counts were 0.126, 0.192, and 0.153 GI/L for the THS 2.2 Menthol, mCC, and SA arms,



respectively. On Day 60, the mean eosinophil counts were 0.124, 0.191, and 0.191 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean eosinophil counts were 0.121, 0.198, and 0.155 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of eosinophil counts for the PP Set are presented in [Figure 47](#).

Figure 47 Forest Plot of Statistical Analysis of Eosinophil Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 5, 30, and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of eosinophil counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0 at all time points.

On Days 5, 30, and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of eosinophil counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points.

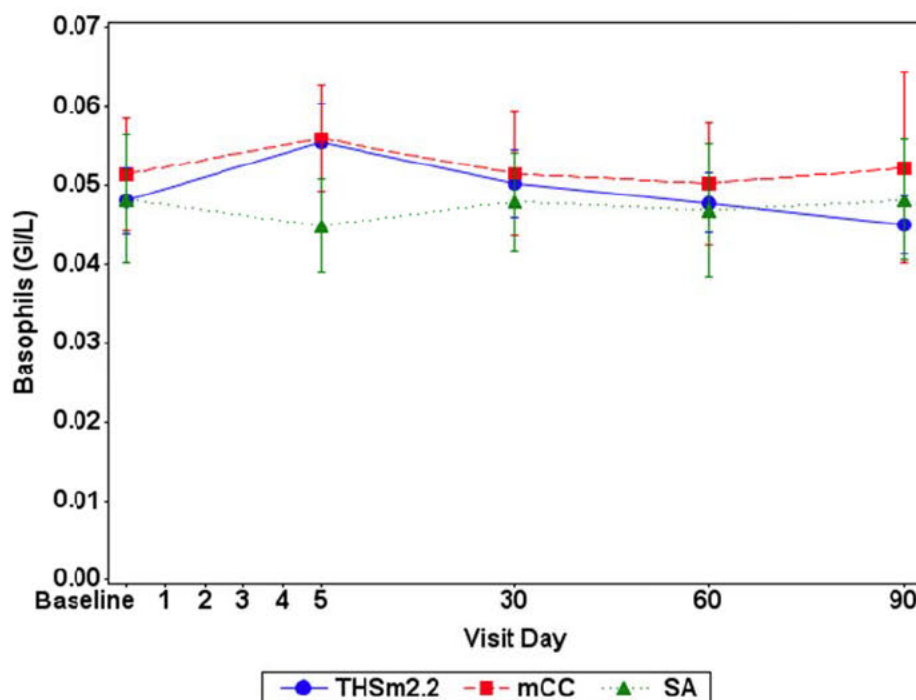
Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.



11.2.6.5.7 Basophil Count (GI/L) During the Study

Data for basophil count for the PP Set are presented in [Figure 48](#).

Figure 48 Arithmetic Mean and 95% CI Basophils (GI/L) During the Course of the Study (PP Set)



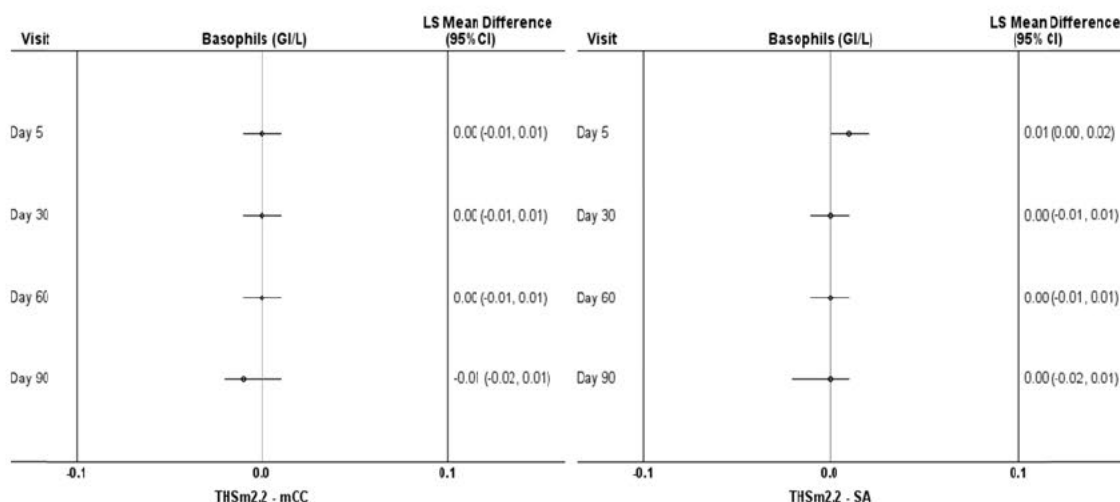
Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.
Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.
Baseline is summarized using the baseline data from the PP Set for Period 1.
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, the mean basophil counts were 0.048, 0.051, and 0.048 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from Confinement Period, the mean basophil counts were 0.056, 0.056, and 0.045 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean basophil counts were 0.050, 0.051, and 0.048 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean basophil counts were 0.048, 0.050, and 0.047 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean basophil counts were 0.045, 0.052, and 0.048 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.



Results of the statistical analysis of basophil counts for the PP Set are presented in [Figure 49](#).

Figure 49 Forest Plot of Statistical Analysis of Basophil Count (GI/L) During the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol. Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 5, 30, and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of basophil counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0 at all time points.

On Days 5, 30, and 60, and the Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of basophil counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0 at all time points.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.6 Risk Markers of Cardiovascular Risk: Homocysteine, hs-CRP, and Fibrinogen During the Study

Subject listings of hs-CRP, homocysteine, and fibrinogen in serum data are provided in [Appendix 15, Listing 15.1.3.2](#).



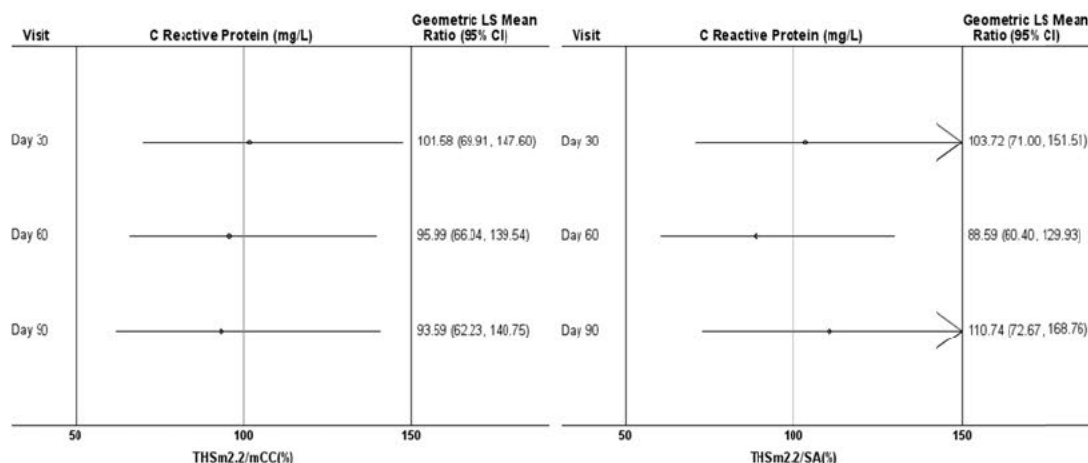
Descriptive statistics of hs-CRP and homocysteine in serum data during the course of the study are provided in [Appendix 15, Table 15.2.4.27.1](#) and [Table 15.2.4.27.2](#) for the PP Set and FAS, respectively, together with changes from baseline. Descriptive statistics of fibrinogen in serum data during the course of the study are provided in [Appendix 15, Table 15.2.4.28.1](#) and [Table 15.2.4.28.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#) and [Figure 15.1.2.3.2](#) for the PP Set and FAS, respectively.

Analyses of hs-CRP, homocysteine, and fibrinogen for THS 2.2 Menthol use versus mCC use, and versus SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The statistical analyses are also presented graphically in [Appendix 15, Figure 15.1.2.2](#).

11.2.6.6.1 hs-CRP (mg/L) During the Study

At baseline (PP Set Period 2), the mean hs-CRP concentrations were 0.203, 0.174, and 0.222 mg/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean hs-CRP concentrations were 0.226, 0.208, and 0.228 mg/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean hs-CRP concentrations were 0.209, 0.205, and 0.244 mg/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 90, the mean hs-CRP concentrations were 0.244, 0.246, and 0.228 mg/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of hs-CRP levels for the PP Set are presented in [Figure 50](#).

**Figure 50 Forest Plot of Statistical Analysis of hs-CRP (mg/L) During the Study (PP Set)**

Abbreviations: CI = confidence intervals; hs-CRP = high sensitive C-reactive protein; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 30, 60, and 90, there were no notable differences observed in the LS means of hs-CRP between subjects who switched to THSm2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 100% at all time points.

On Day 30, there were no notable differences observed in the LS means of hs-CRP between subjects who switched to THSm2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100% at all time points.

On Day 60, the LS means of hs-CRP in subjects who switched to THSm2.2 Menthol use were 11.41% lower than that observed in subjects who abstained from smoking (95% CI: 60.40, 129.93).

On Day 90, the LS means of hs-CRP in subjects who switched to THSm2.2 Menthol use were 10.74% higher than that observed in subjects who abstained from smoking (95% CI: -27.33, 68.76).

Analysis using the FAS showed consistent results to those presented.

11.2.6.6.2 Homocysteine (umol/L) During the Study

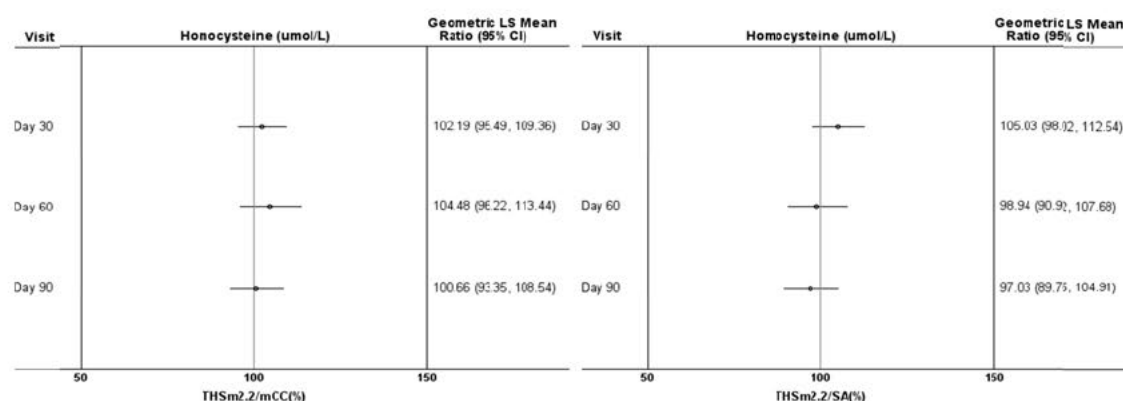
At baseline (PP Set Period 2), the mean homocysteine concentrations were 10.224, 10.938, and 11.316 umol/L for the THSm2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean homocysteine concentrations were 11.045, 11.498, and



11.563 $\mu\text{mol/L}$ for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean homocysteine concentrations were 10.693, 10.656, and 11.514 $\mu\text{mol/L}$ for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 90, the mean homocysteine concentrations were 11.568, 12.052, and 12.885 $\mu\text{mol/L}$ for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of homocysteine for the PP Set are presented in [Figure 51](#).

Figure 51 Forest Plot of Statistical Analysis of Homocysteine ($\mu\text{mol/L}$) During the Ambulatory Period (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 30, 60, and 90, there were no notable differences observed in the LS means of homocysteine between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 100% at all time points.

On Days 30, 60, and 90, there were no notable differences observed in the LS means of homocysteine between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with 95% CIs spanning 100% at all time points.

Analysis using the FAS showed consistent results to those presented.

11.2.6.6.3 Fibrinogen (mg/dL) During the Study

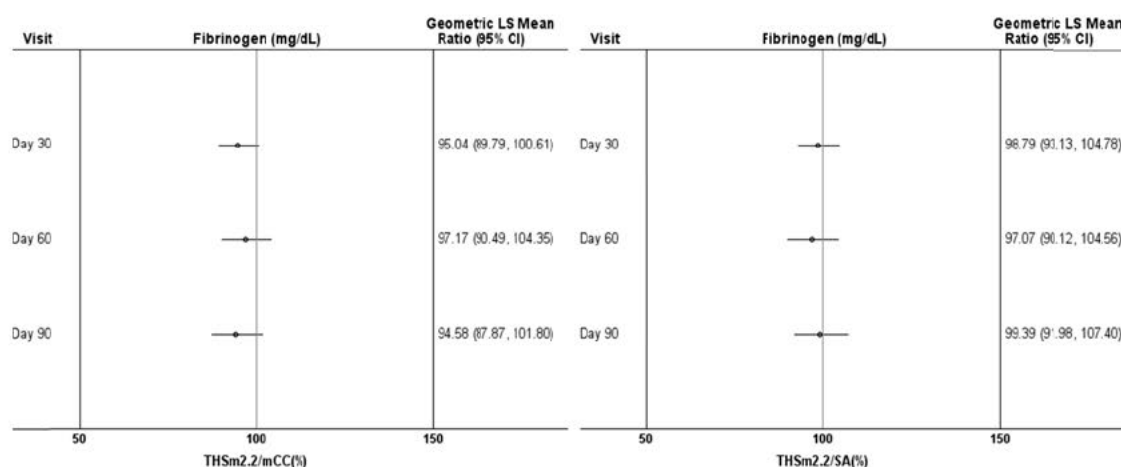
At baseline (PP Set Period 2), the mean fibrinogen concentrations were 278.73, 276.16, and 285.65 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean fibrinogen concentrations were 277.00, 286.98, and 283.63 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean fibrinogen



concentrations were 273.16, 278.14, and 279.55 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 90, the mean fibrinogen concentrations were 275.91, 286.14, and 277.63 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of fibrinogen for the PP Set are presented in [Figure 52](#).

Figure 52 Forest Plot of Statistical Analysis of Fibrinogen (mg/dL) During the Ambulatory Period (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Figure 15.1.2.2](#)

On Days 30, 60, and 90, there were no notable differences observed in the LS means of fibrinogen between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 100% at all time points.

On Days 30, 60, and 90, there were no notable differences observed in the LS means of fibrinogen between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with 95% CIs spanning 100% at all time points.

Analysis using the FAS showed consistent results to those presented.

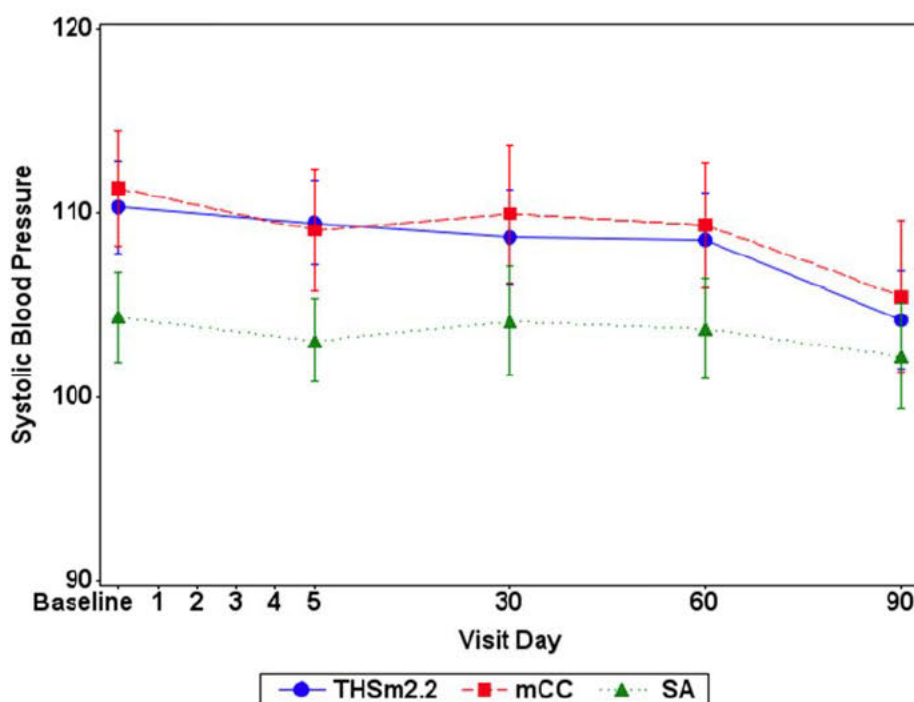
11.2.6.7 Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure During the Study

Subject listings of systolic and diastolic blood pressure data are provided in [Appendix 15, Listing 15.3.6.7](#).



Descriptive statistics of systolic and diastolic blood pressure during the course of the study are provided in [Appendix 15, Table 15.2.4.26.1](#) and [Table 15.2.4.26.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results for the PP Set are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#), and in [Figure 53](#) and [Figure 54](#) for systolic and diastolic blood pressure, respectively. The results for the FAS are presented graphically in [Appendix 15, Figure 15.1.2.3.2](#).

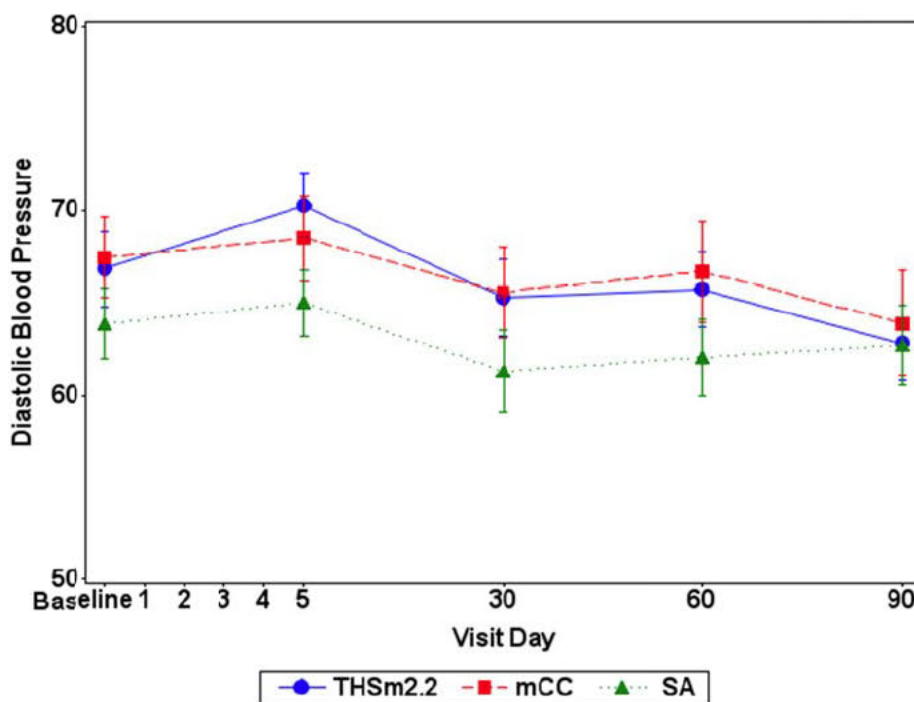
Figure 53 Arithmetic Mean and 95% CI Systolic Blood Pressure (mmHg) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline is summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.3.1](#)



Figure 54 Arithmetic Mean and 95% CI Diastolic Blood Pressure (mmHg) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#)

At baseline, mean systolic blood pressure was 110.3, 111.4, and 104.4 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Confinement Period, mean systolic blood pressure was 109.5, 109.1, and 103.1 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, mean systolic blood pressure was 108.7, 110.0, and 104.1 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, mean systolic blood pressure was 108.5, 109.4, and 103.7 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day of Discharge from the Ambulatory Period, mean systolic blood pressure was 104.2, 105.5, and 102.2 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively.

At baseline, mean diastolic blood pressure was 66.9, 67.5, and 63.9 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Confinement Period, mean diastolic blood pressure was 70.3, 68.5, and 65.0 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, mean diastolic blood

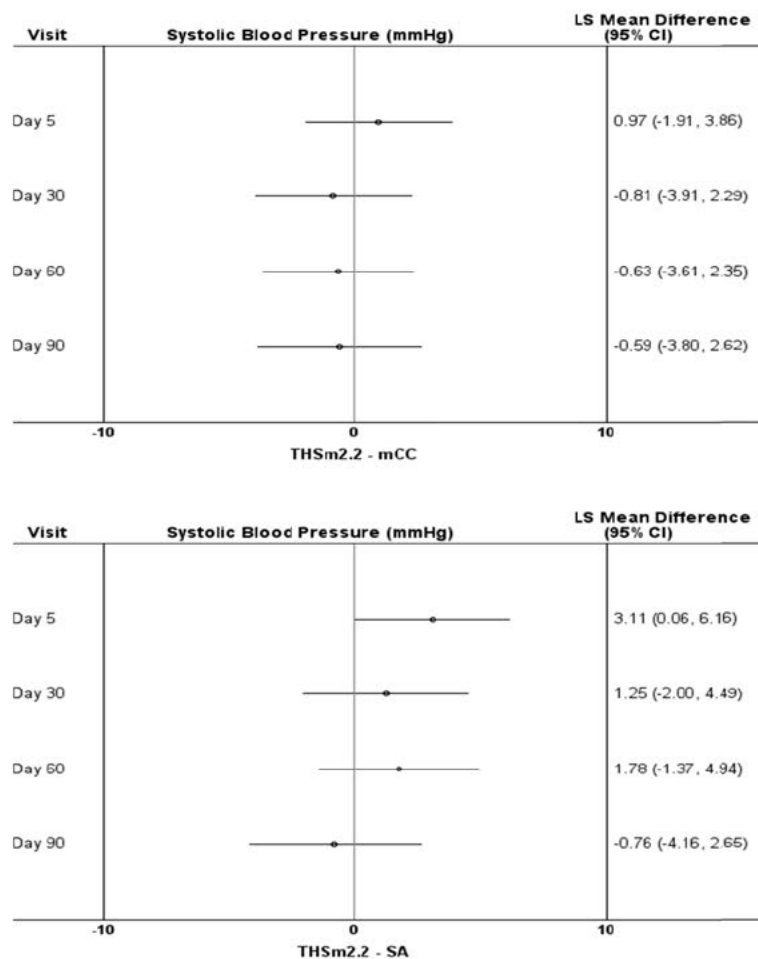


pressure was 65.3, 65.6, and 61.3 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, mean diastolic blood pressure was 65.7, 66.7, and 62.1 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day of Discharge from the Ambulatory Period, mean diastolic blood pressure was 62.8, 63.9, and 62.7 mmHg for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Analyses for systolic and diastolic blood pressure for the THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The analyses for the PP Set are graphically presented in [Appendix 15, Figure 15.1.2.2](#) and in [Figure 55](#) and [Figure 56](#), for systolic and diastolic blood pressure, respectively. In addition, analyses of systolic and diastolic blood pressure are tabulated in [Table 110](#) and [Table 111](#) for Days 5 and 90, respectively.



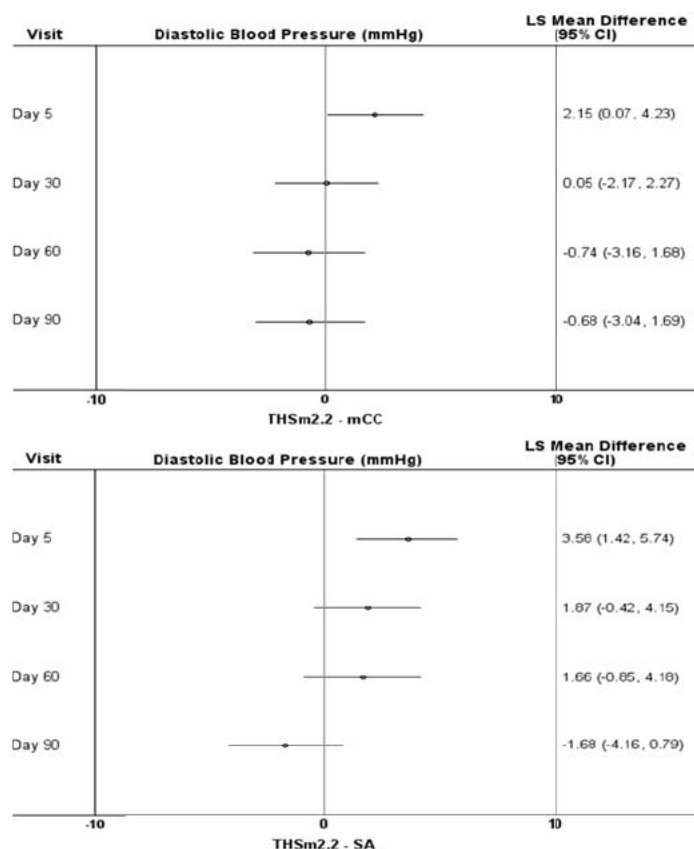
Figure 55 Forest Plot of Statistical Analysis of Systolic Blood Pressure (mmHg) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Figure 15.1.2.2.](#)



Figure 56 Forest Plot of Statistical Analysis of Diastolic Blood Pressure (mmHg) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Figure 15.1.2.2](#).

**Table 110 Analysis of Systolic and Diastolic Blood Pressure versus mCC and SA on Day of Discharge (Confinement Period) (PP Set)**

Parameter	Exposure	Number of Subjects	Arithmetic LS Mean	LS Mean Difference (THS m2.2 versus mCC and SA)	95% CI
Systolic blood pressure (mmHg)	THS m2.2	76	108.71	0.97	-1.91, 3.86
	mCC	42	107.73		
	THS m2.2	76	108.71	3.11	0.06, 6.16
	SA	39	105.60		
Parameter	Exposure	Number of Subjects	Arithmetic LS Mean	LS Mean Difference (THS m2.2 versus mCC and SA)	95% CI
Diastolic blood pressure (mmHg)	THS m2.2	76	69.94	2.15	0.07, 4.23
	mCC	42	67.79		
	THS m2.2	76	69.94	3.58	1.42, 5.74
	SA	39	66.36		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#)

On the Day of Discharge from the Confinement Period, the LS means of systolic blood pressure were comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CI spanning 0.

On the Day of Discharge (Confinement), the LS mean of systolic blood pressure in subjects who switched to THS 2.2 Menthol use was 3.11 mmHg higher than that observed in subjects who abstained from smoking (95% CI: 0.06, 6.16).

On the Day of Discharge (Confinement), the LS mean of diastolic blood pressure in subjects who switched to THS 2.2 Menthol use was 2.15 mmHg higher than that observed in subjects who continued to smoke mCC (95% CI: 0.07, 4.23) and 3.58 mmHg higher than that observed in subjects who abstained from smoking (95% CI: 1.42, 5.74).



Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

Table 111 Analysis of Systolic and Diastolic Blood Pressure versus mCC and SA on Day of Discharge (Ambulatory Period) (PP Set)

Parameter	Exposure	Number of Subjects	Arithmetic LS Mean	LS Mean Difference (THS m2.2 versus mCC and SA)	95% CI
Systolic blood pressure (mmHg)	THS m2.2	70	103.17		
	mCC	41	103.76	-0.59	-3.80, 2.62
	THS m2.2	70	103.17		
	SA	37	103.92	-0.76	-4.16, 2.65
	THS m2.2	70	62.25		
	mCC	41	62.93	-0.68	-3.04, 1.69
Diastolic blood pressure (mmHg)	THS m2.2	70	62.25		
	mCC	41	62.93	-0.68	-3.04, 1.69
	THS m2.2	70	62.25		
	SA	37	63.93	-1.68	-4.16, 0.79
	THS m2.2	70	62.25		
	mCC	41	62.93	-0.68	-3.04, 1.69

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.25.1](#)

On Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of systolic and diastolic blood pressure between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 0.

On Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of systolic and diastolic blood pressure between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.



11.2.6.8 Risk Markers of Metabolic Syndrome: Blood Glucose, Body Weight, Waist Circumference, and Hb1Ac During the Study

11.2.6.8.1 Body Weight and Waist Circumference During the Study

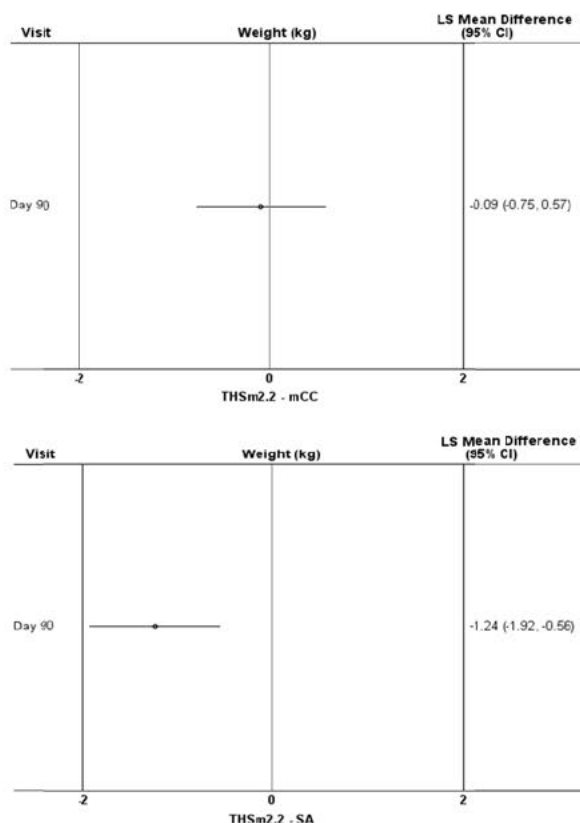
Subject listings of weight details are provided in [Appendix 15, Listing 15.3.6.7](#).

Descriptive statistics of body weight and waist circumference during the study are provided in [Appendix 15, Table 15.2.4.33.1](#) and [Table 15.2.4.33.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results for the PP Set are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#) and [Figure 15.1.2.3.2](#) for the PP Set and FAS, respectively.

Analyses of body weight and waist circumference for THS 2.2 Menthol use versus mCC use and SA on Day of Discharge from the Ambulatory Period are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The analyses for the PP Set are also presented graphically in [Appendix 15, Figure 15.1.2.2](#) and in [Figure 57](#) and [Figure 58](#), for weight and waist circumference, respectively.



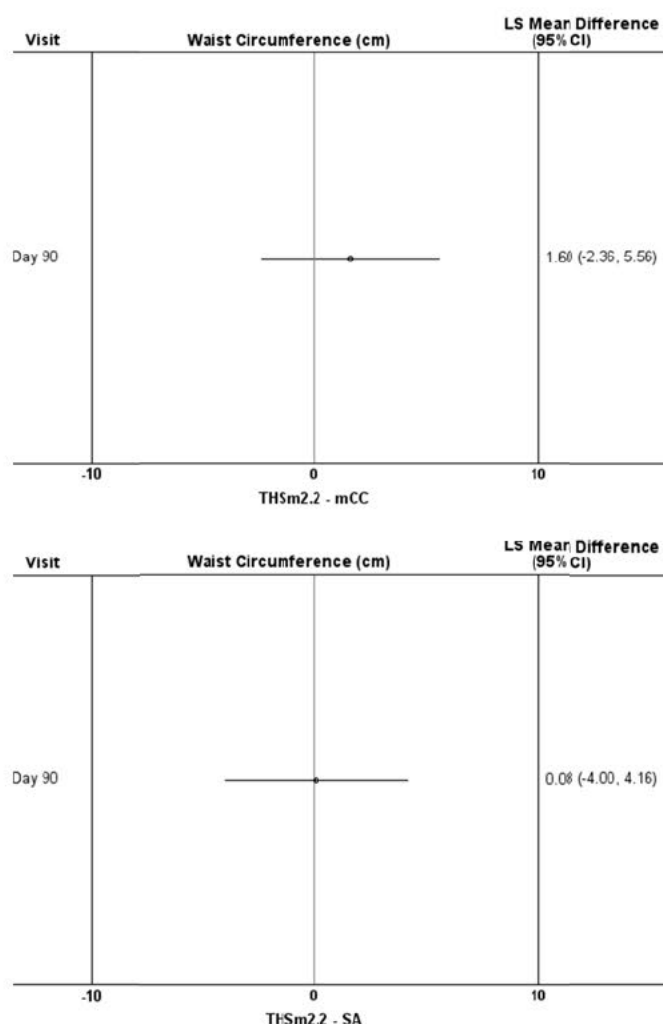
Figure 57 Forest Plot of Statistical Analysis of Weight (kg) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; TBSm2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Figure 15.1.2.2.](#)



Figure 58 Forest Plot of Statistical Analysis of Waist Circumference (cm) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Figure 15.1.2.2.](#)

On the Day of Discharge (Ambulatory), there was no notable difference in LS means of weight or waist circumference between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with 95% CIs spanning 0.

On the Day of Discharge (Ambulatory), there was no notable difference observed in the LS means of waist circumference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0. The LS mean of



weight in subjects who switched to THS 2.2 Menthol use was 1.24 kg lower than that observed in subjects who abstained from smoking, with 95% CI: -1.92, -0.56.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.8.2 Blood Glucose During the Study

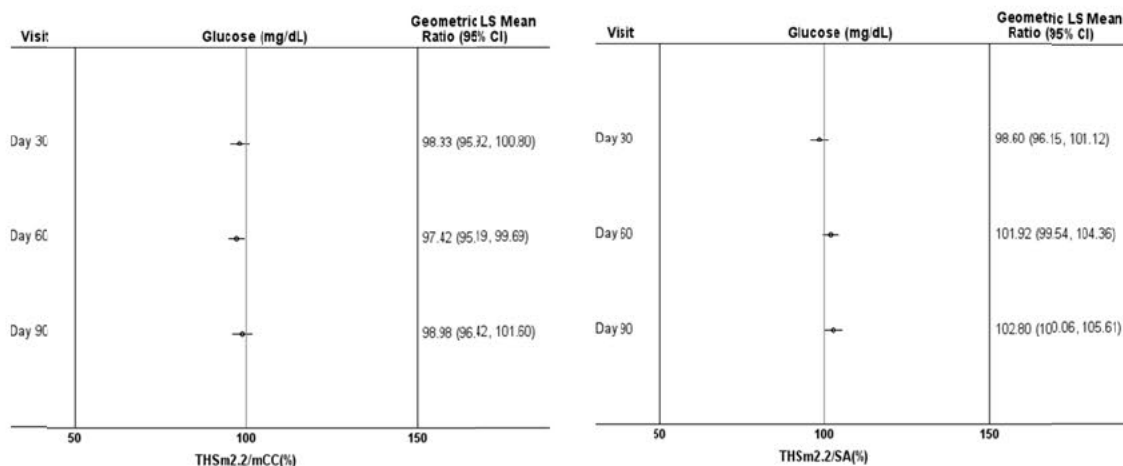
Subject listings of blood glucose in serum data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of blood glucose in serum data during the study are provided in [Appendix 15, Table 15.2.4.27.1](#) and [Table 15.2.4.27.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results for the PP Set are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#). The results for the FAS are presented graphically in [Appendix 15, Figure 15.1.2.3.2](#).

Analyses of blood glucose for THS 2.2 Menthol use versus mCC use and SA during the study are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The analyses for the PP Set are also presented graphically in [Figure 59](#) and [Appendix 15, Figure 15.1.2.2](#).



Figure 59 Forest Plot of Statistical Analysis of Blood Glucose (mg/dL) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2](#)

At baseline, the mean concentrations for blood glucose were 84.6, 85.4, and 84.9 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 30, the mean concentrations for blood glucose were 89.9, 91.9, and 91.3 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On Day 60, the mean concentrations for blood glucose were 89.8, 92.4, and 88.2 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively. On the Day of Discharge from the Ambulatory Period, the mean concentrations for blood glucose were 89.8, 91.1, and 87.6 mg/dL for the THS 2.2 Menthol, mCC, and SA arms, respectively.

On Day 30 and Day of Discharge (Ambulatory), there were no notable differences observed in the LS means of blood glucose between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 100%. On Day 60, the LS mean of blood glucose in subjects who switched to THS 2.2 Menthol use was 2.58% lower than that of subject who continued to smoke mCC (95% CI: 0.31, 4.81; [Figure 59](#)).

On Days 30 and 60, there were no notable differences observed in the LS means of blood glucose between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 100% at both time points. On Day of Discharge (Ambulatory), the LS mean in subjects who switched to THS 2.2 Menthol use was 2.80% higher than that observed in subjects who abstained from smoking (95% CI: 0.05, 5.61) ([Figure 59](#)).



Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.2.6.8.3 Hb1Ac During the Study

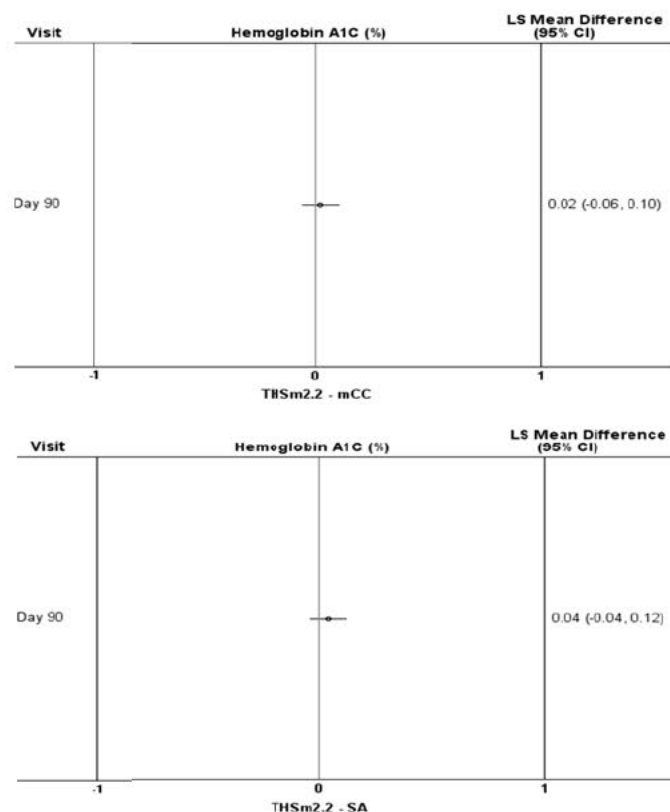
Subject listings of HbA1c data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of Hb1Ac during the study are provided in [Appendix 15, Table 15.2.4.29.1](#) and [Table 15.2.4.29.2](#) for the PP Set and FAS, respectively, together with changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#) and [Figure 15.1.2.3.2](#) for the PP Set and FAS, respectively.

Analyses for THS 2.2 Menthol use versus mCC use and SA on Day 90 are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively. The results are also presented graphically in [Appendix 15, Figure 15.1.2.2](#) and presented in [Figure 60](#).



Figure 60 Forest Plot of Statistical Analysis of HbA1c (%) During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; HbA1c = hemoglobin A1c; LS = least squares; mCC = menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2](#).

On Day 90, there were no notable differences observed in the LS means of HbA1c between subjects who switched to THSm2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI spanning 0.

On Day 90, there were no notable differences observed in the LS means of HbA1c between subjects who switched to THSm2.2 Menthol use and subjects who abstained from smoking, with the 95% CI spanning 0.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.



11.2.6.9 Risk Markers Associated with Respiratory Diseases

Analyses of FEV₁ (% pred) without bronchodilator for THS 2.2 Menthol use versus mCC use and SA on the Day of Discharge from the Ambulatory Period are tabulated in [Appendix 15, Table 15.2.4.25.1.2](#) for the PP Set.

The results showed LS mean values of 95.36 (95% CI: 94.11, 96.62) for the THS 2.2 Menthol arm, 93.45 (95% CI: 91.81, 95.09) for the mCC arm, and 95.38 (95% CI: 93.66, 97.11) for the SA arm.

The THS m2.2 – mCC difference was 1.91 (95% CI: -0.14; 3.97), and the THS m2.2 – SA difference was -0.02 (95% CI: -2.15, 2.11).

11.3 Analysis of Exploratory Endpoints During the Study

11.3.1 Ames Mutagenicity Test During the Study

Individual subject listings of mutagenicity results and changes from baseline data are provided in [Appendix 15, Listing 15.3.5.1](#). Descriptive statistics of Ames mutagenicity test (YG1024+S9) including change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.46.1](#) and [Table 15.2.4.46.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 112](#) for the Confinement Period and in [Table 113](#) for the Ambulatory Period.

Table 112 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (REV/24h) During the Confinement Period (PP Set)

Study Arm	Time Point	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS m2.2	Baseline	65	17293.80	12542.53	0.0	13943.72	51505.1
	Day 5	73	7500.05	8886.202	0.0	4856.25	47872.0
mCC	Baseline	38	15132.36	10702.14	2331.6	13235.99	51400.0
	Day 5	40	13476.64	7826.005	0.0	13578.55	39632.9
SA	Baseline	35	14508.13	10211.61	0.0	14000.04	44541.2
	Day 5	37	9237.10	10000.88	0.0	6385.80	44541.2

Abbreviations: Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.46.1](#).



At baseline, mean Ames mutagenicity test values were consistent between the THS 2.2 Menthol and mCC arms (17293.80 and 15132.36 REV/24h, respectively) and lower in the SA arm (14508.13 REV/24h). On Day 5, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values were approximately 2.3-fold and 1.6-fold lower than baseline; while in the mCC arm, mean Ames mutagenicity test values (REV/24h) were approximately 1.1-fold lower than baseline (Table 112). Consistent results were also observed in median values, with values on Day 5 2.9- and 2.2-fold lower than baseline in the THS 2.2 Menthol and SA arms, respectively, and 0.97-fold higher than baseline in the mCC arm.

Table 113 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (REV/24h) During the Ambulatory Period (PP Set)

Study Arm	Time Point	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS m2.2	Baseline	65	17293.80	12542.53	0.0	13943.72	51505.1
	Day 90	70	6761.03	6689.370	0.0	5399.62	47872.0
mCC	Baseline	38	15132.36	10702.14	2331.6	13235.99	51400.0
	Day 90	40	17204.22	12257.97	0.0	13192.79	47824.0
SA	Baseline	35	14508.13	10211.61	0.0	14000.04	44541.2
	Day 90	37	8136.60	8523.113	0.0	4977.36	35588.0

Abbreviations: Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.46.1](#).

On Day 90, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values were approximately 2.6- and 1.8-fold lower than baseline, respectively; while in the mCC arm, mean Ames mutagenicity test values were approximately 1.1-fold higher than baseline (Table 113). Consistent results were also observed in median values, with values approximately 2.6-, 1.0-, and 2.8-fold lower than baseline on Day 90 in the THS 2.2 Menthol, mCC, and SA arms, respectively.

11.3.2 Cytochrome P450 2A6 Activity During the Study

Cytochrome P450 2A6 activity was calculated in plasma as the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.

Individual subject listings of CYP2A6 activity and changes from baseline data are provided in [Appendix 15, Listing 15.3.6.16](#). Descriptive statistics of CYP2A6 activity



including change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.44.1](#) and [Table 15.2.4.44.2](#) for the PP Set and FAS, respectively. Data for the PP Set are provided in [Table 114](#) and [Table 115](#). In addition, descriptive statistics excluding any assessments taken within 5 half-lives of a concomitant medication known to impact CYP2A6 activity were summarized in [Appendix 15, Table 15.2.4.44.1.1](#) and [Table 15.2.4.44.2.1](#) for the PP Set and FAS, respectively.

Table 114 Descriptive Statistics of Percent Change from Baseline in CYP2A6 Activity (%) (PP Set)

Study Arm	Time Point	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS m2.2	Day 5 % change from baseline	76	11.44	16.236	-68.4	10.62	45.6
mCC	Day 5 % change from baseline	42	11.95	15.104	-21.1	11.77	39.6
SA	Day 5 % change from baseline	39	237.55	180.132	55.6	206.11	1111.9

Abbreviations: CYP2A6 = cytochrome P450 2A6; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

% change from baseline, where baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.44.1](#).

At baseline, CYP2A6 activity was comparable between study arms (range of 26.05% to 28.53%). In the THS 2.2 Menthol and mCC arms, CYP2A6 increased by approximately 11% and 12%, respectively on the Day of Discharge from Confinement Period. In the SA arm, CYP2A6 activity increased by approximately 2.38-fold (median value of 206.11%). No assessments were excluded in the Confinement Period as no concomitant medication that was known to impact CYP2A6 activity had been taken within 5 half-lives of a CYP2A6 assessment.

**Table 115 Descriptive Statistics of Percent Change from Baseline in CYP2A6 Activity (%) (PP Set)**

Study Arm	Time Point	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS m2.2	Day 90 % change from baseline	70	5.32	25.640	-71.5	2.56	111.1
mCC	Day 90 % change from baseline	41	3.14	18.610	-29.0	1.66	54.5
SA	Day 90 % change from baseline	37	181.30	293.939	-97.9	40.12	1330.1

Abbreviations: CYP2A6 = cytochrome P450 2A6; Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SA = smoking abstinence; SD = standard deviation; THS m2.2 = Tobacco Heating System 2.2 Menthol.

% change from baseline, where baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.44.1](#)

In the THS 2.2 Menthol and mCC arms, CYP2A6 increased by approximately 3% to 5% on Day 90. In the SA arm, CYP2A6 activity increased by approximately 1.81-fold (median of 40.12%). There was only 1 assessment excluded from the THS 2.2 Menthol arm due to being within 5 half-lives of concomitant medications that impact CYP2A6 activity, and thus the results were consistent with those results when no assessments were excluded.

Analyses of CYP2A6 activity (absolute) on the Day of Discharge (Confinement) and Day 90 for THS 2.2 Menthol use versus mCC use, and versus SA, are tabulated in [Appendix 15, Table 15.2.4.45.1](#) and [Table 15.2.4.45.2](#), for the PP Set and FAS, respectively.

Data for the PP Set was also provided in [Table 116](#) and [Table 117](#) for the Day of Discharge (Confinement) and Day 90, respectively.

**Table 116 Analysis of CYP2A6 Activity (%) versus mCC and SA on Day of Discharge (Confinement) (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Day 6/Discharge Confinement	THS m2.2	76	24.85	98.39	24.69	89.67, 107.96
	mCC	42	25.26			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Day 6/Discharge Confinement	THS m2.2	76	24.85	35.67	24.69	32.44, 39.22
	SA	39	69.67			

Abbreviations: CYP2A6 = cytochrome P450 2A6; mCC = Menthol conventional cigarette; CI = confidence interval; CV = coefficient of variation; PP = per protocol; LS = least squares; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.45.1](#).

There was no notable difference in LS means for absolute CYP2A6 activity on the Day of Discharge (Confinement) between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI for the LS mean ratio spanning 100%.

On the Day of Discharge (Confinement), the LS mean of absolute CYP2A6 activity following THS 2.2 Menthol use was 64.33% lower than the activity observed in subjects who abstained from smoking (95% CI: 60.78, 67.56).

**Table 117 Analysis of CYP2A6 Activity (%) versus mCC and SA on Day 90 (PP Set)**

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
THS m2.2	70	22.70	98.73	61.36	79.17, 123.12
mCC	41	22.99			

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
THS m2.2	70	22.70	55.79	61.36	44.44, 70.02
SA	37	40.68			

Abbreviations: CYP2A6 = cytochrome P450 2A6; mCC = Menthol conventional cigarette; CI = confidence interval; CV = coefficient of variation; PP = per protocol; LS = least squares; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.45.1](#).

There was no notable difference in the LS mean of CYP2A6 activity on Day 90 between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI for the LS mean ratio spanning 100%.

On Day 90, the LS mean of CYP2A6 activity following THS 2.2 Menthol use was 44.21% lower than the activity observed in subjects who abstained from smoking (95% CI: 29.98, 55.56).

11.3.3 Fagerström Test for Nicotine Dependence During the Study

Individual subject responses to the FTND are tabulated by study arm in [Appendix 15, Listing 15.3.6.11](#).

The FTND overall classification is summarized by category (mild: 0 to 3; moderate: 4 to 6; severe: 7 to 10) at baseline (Period 4) and Day 90, along with shifts from baseline, for the PP Set, FAS, and Compliant Population in [Appendix 15, Table 15.2.4.34.1](#), [Table 15.2.4.34.2](#), and [Table 15.2.4.34.3](#), respectively. Data presented in [Table 118](#) are for the PP Set.

**Table 118 Fagerström Test of Nicotine Dependence (PP Set Period 4)**

Timepoint FTND Score	Statistic	Study Arm		
		THS m2.2 (N=70)	mCC (N=41)	SA (N=37)
Baseline				
	N	70	41	36
	Mean	4.3	4.3	4.7
	SD	1.78	1.82	2.13
	Median	4.0	4.0	5.0
	Min, Max	1, 8	1, 8	0, 9
Mild (n [%])		26 (37.1)	17 (41.5)	8 (21.6)
Moderate (n [%])		38 (54.3)	17 (41.5)	21 (56.8)
Severe (n [%])		6 (8.6)	7 (17.1)	7 (18.9)
Day 90				
	N	69	41	37
	Mean	4.1	3.6	3.2
	SD	2.10	1.71	2.52
	Median	4.0	4.0	3.0
	Min, Max	0, 9	0, 7	0, 8
Mild (0 – 3) , n(%)		28 (40.0)	17 (41.5)	20 (54.1)
[1] Mild to Mild, n(%)		18 (25.7)	12 (29.3)	7 (18.9)
[1] Moderate to Mild, n(%)		9 (12.9)	4 (9.8)	11 (29.7)
[1] Severe to Mild, n(%)		1 (1.4)	1 (2.4)	2 (5.4)
Moderate (4 – 6) , n(%)		33 (47.1)	22 (53.7)	14 (37.8)
[1] Mild to Moderate, n(%)		8 (11.4)	5 (12.2)	1 (2.7)
[1] Moderate to Moderate, n(%)		25 (35.7)	13 (31.7)	9 (24.3)
[1] Severe to Moderate, n(%)		0	4 (9.8)	4 (10.8)
Severe (7 – 10), n(%)		8 (11.4)	2 (4.9)	3 (8.1)
[1] Moderate to Severe, n(%)		3 (4.3)	0	1 (2.7)
[1] Severe to Severe, n(%)		5 (7.1)	2 (4.9)	1 (2.7)

Abbreviations: FTND = Fagerström Test of Nicotine Dependence; max = maximum; min = minimum; mCC = Menthol conventional cigarette; N = number of subjects; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

[1] change/shift from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Data Source: [Appendix 15, Table 15.2.4.34.1](#)

Within the PP Set, for the THS 2.2 Menthol and the mCC arms, the majority of subjects had no apparent shift in FTND score, with 25 subjects (35.7%) for the THS 2.2 Menthol arm and 13 subjects (31.7%) for the mCC arm reporting a moderate dependence on nicotine at baseline and a moderate dependence on nicotine on Day 90. In the SA arm, the



highest proportion of subjects (29.7%) reported a moderate dependence at baseline and a mild dependence on Day 90.

In the THS 2.2 Menthol arm, the next most frequent shifts in FTND were mild to mild (18 subjects [25.7%]), moderate to mild (9 subjects [12.9%]), and mild to moderate (8 subjects [11.4%]) between baseline and Day 90. There were 3 subjects who shifted from moderate to severe (4.3%) and 5 subjects who did not change from a baseline assessment of severe (severe to severe [7.1%]) in the THS 2.2 Menthol arm. In addition, 2 subjects of the mCC arm and 1 subject of the SA arm did not shift from their baseline assessments of severe (severe to severe).

Similar results were also observed for the FAS and Compliant Population.

11.3.4 Subjective Effects of Smoking Endpoints During the Study

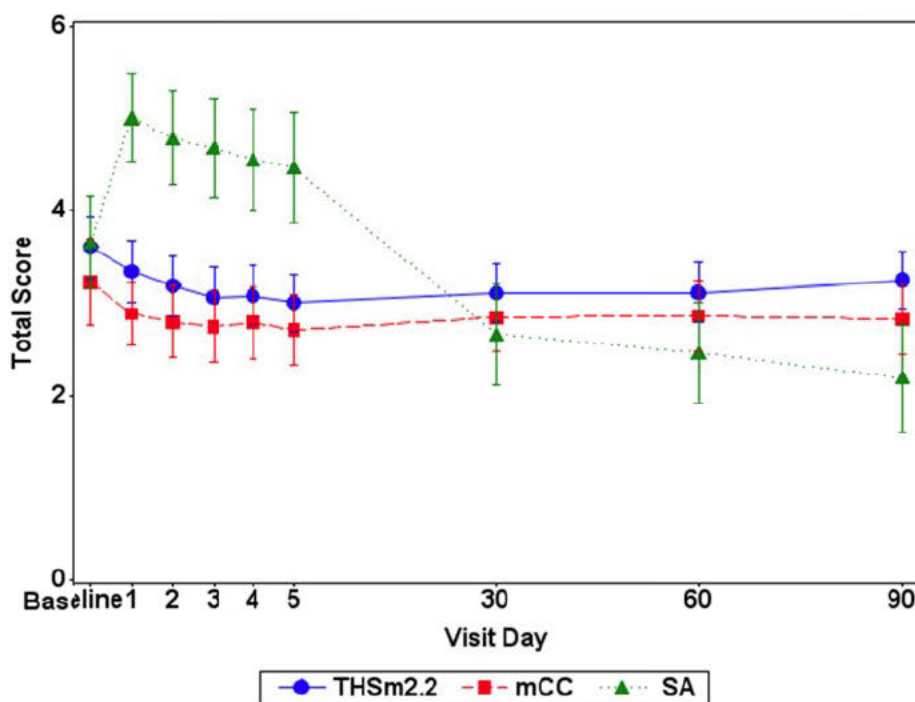
11.3.4.1 Urge-to-Smoke Symptoms (QSU-brief) During the Study

Responses to the QSU-brief questionnaire used to measure urge-to-smoke symptoms, 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 15.3.6.12](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.35.1](#) and [Table 15.2.4.35.2](#) for the PP Set and the FAS, respectively.

Line graphs showing the arithmetic mean total scores and 95% CI for the QSU-brief over the course of the study are presented in [Appendix 15, Figure 15.1.2.4.1](#) and [15.1.2.4.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Figure 61](#).



Figure 61 Arithmetic Mean and 95% CI Total Scores for QSU-Brief During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; PP = per protocol; QSU-Brief = questionnaire of smoking urges (brief version); SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

QSU-Brief scores reported on a 7-point scale. Higher values indicate greater intensity of urge.

Data Source: [Appendix 15, Figure 15.1.2.4.1](#).

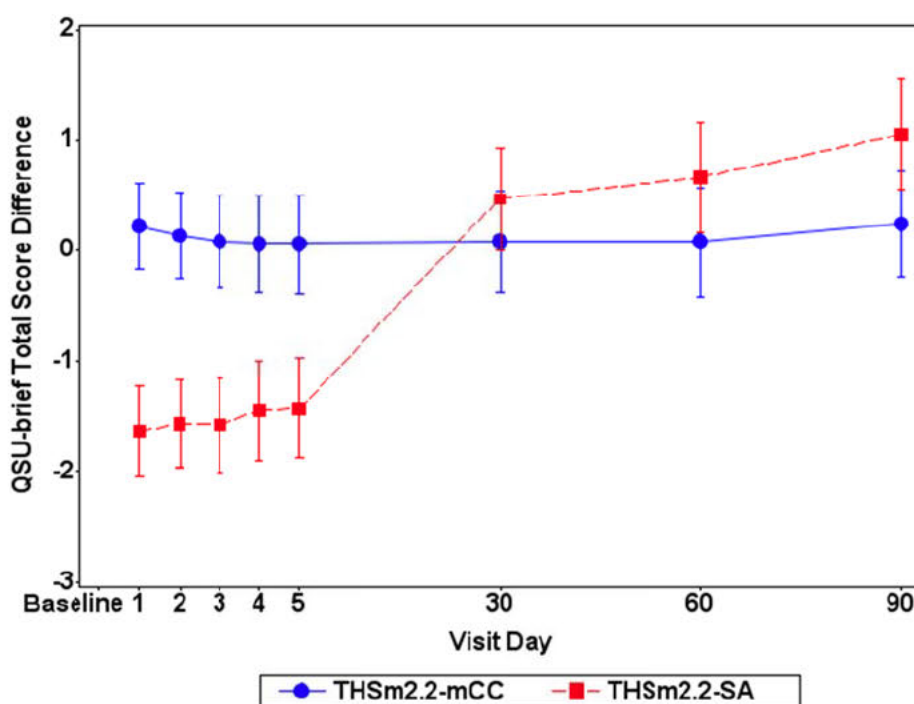
The mean urge-to-smoke total scores were 3.60 for the THS 2.2 Menthol arm, 3.22 for the mCC arm and 3.65 for the SA arm at baseline. For the THS 2.2 Menthol and mCC arms, the mean urge-to-smoke total scores remained stable over the 5 days of the Confinement Period (ranges of individual scores of 1.0 to 6.0 and 1.0 to 5.9, respectively). In the SA arm, the mean urge-to-smoke total score increased from baseline to 5.01 on Day 1 (corresponding to a mean increase of 52.19%). From Day 2 to 5, total score values continuously decreased, with a value of 4.47 on Day 5.

During the Ambulatory Period, the mean urge-to-smoke total scores remained stable compared to baseline for THS 2.2 Menthol, mCC, and SA arms, with Day 90 values of 3.25, 2.83, and 2.19, respectively.



The results from the statistical analysis of the QSU-brief questionnaire factors and total score are tabulated in [Appendix 15, Table 15.2.4.36.1](#) and [Table 15.2.4.36.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 119](#) and [Table 120](#). Profiles of the LS mean differences (THS m2.2 – mCC and THS m2.2 – SA) over time are presented in [Appendix 15, Figure 15.1.2.5.1](#) (total score) and in [Figure 62](#), for the PP Set.

Figure 62 Mean and 95% CI Total Scores Least Squares Means Differences for QSU-Brief During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; QSU-brief = questionnaire of smoking urges (brief version); PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol; Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. QSU-brief scores reported on a 7-point scale. Higher values indicate greater intensity of urge. Data Source: [Appendix 15, Figure 15.1.2.5.1](#)

The mean LS mean differences of THS 2.2 Menthol – mCC for urge-to-smoke total scores remained stable through the Confinement Period, with a difference of 0.22 on Day 1 and 0.06 on Day 5. The mean LS mean differences of THS 2.2 Menthol – SA for urge-to-smoke total scores was -1.64 on Day 1 and -1.43 on Day 5 ([Figure 62](#)).



During the Ambulatory Period, the mean LS mean differences of THS 2.2 Menthol – mCC for urge-to-smoke total scores remained stable, with a difference of 0.24 on Day 90. Whereas, the mean LS mean differences of THS 2.2 Menthol – SA for urge-to-smoke total scores were 0.47, 0.67, and 1.06 on Days 30, 60, and 90, respectively (Figure 62).

Table 119 Analysis of QSU-brief Questionnaire Factors and Total Score on Day 5 (PP Set)

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Total	Day 5	THS m2.2	75	2.95	0.06	-0.39, 0.50
		mCC	41	2.90		
Factor 1	Day 5	THS m2.2	75	3.45	0.04	-0.47, 0.55
		mCC	41	3.41		
Factor 2	Day 5	THS m2.2	75	2.47	0.10	-0.34, 0.54
		mCC	41	2.37		

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Total	Day 5	THS m2.2	75	2.95	-1.43	-1.88, -0.98
		SA	39	4.38		
Factor 1	Day 5	THS m2.2	75	3.45	-1.35	-1.87, -0.84
		SA	39	4.80		
Factor 2	Day 5	THS m2.2	75	2.47	-1.50	-1.95, -1.05
		SA	39	3.97		

Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; LS = least squares; PP = per protocol; QSU-brief = questionnaire of smoking urges (brief version); SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, mCC consumption reported at Screening as fixed effect factors.

Data Source: Appendix 15, Table 15.2.4.36.1.

On Day 5, there were no notable differences in the LS means of QSU-brief urge-to-smoke total scores, Factor 1 scores, or Factor 2 scores between the subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, with 95% CIs for all parameters spanning 0.



The urge-to-smoke overall and factor scores of subjects who switched to THS 2.2 Menthol use were lower than those subjects who abstained from smoking, with LS mean differences of -1.43 points (95% CI: -1.88, -0.98), -1.35 points (95% CI: -1.87, -0.84), and -1.50 points (95% CI: -1.95, -1.05) for QSU-brief total score, Factor 1 score, and Factor 2 score, respectively.

Table 120 Analysis of QSU-brief Questionnaire Factors and Total Score on Day 90 (PP Set)

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Total	Day 90	THS m2.2	69	3.18	0.24	-0.25, 0.72
		mCC	41	2.94		
Factor 1	Day 90	THS m2.2	69	3.85	0.37	-0.19, 0.94
		mCC	41	3.47		
Factor 2	Day 90	THS m2.2	69	2.53	0.12	-0.34, 0.58
		mCC	41	2.41		

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Total	Day 90	THS m2.2	69	3.18	1.06	0.56, 1.55
		SA	37	2.12		
Factor 1	Day 90	THS m2.2	69	3.85	1.50	0.92, 2.07
		SA	37	2.35		
Factor 2	Day 90	THS m2.2	69	2.53	0.63	0.16, 1.10
		SA	37	1.89		

Abbreviations: ANCOVA = analysis of covariance; mCC = Menthol conventional cigarette; CI = confidence interval; LS = least squares; QSU-brief = questionnaire of smoking urges (brief version); SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.36.1](#).

During the Ambulatory Period, considering the overall and factor scores, there were differences between the LS means QSU-brief urge-to-smoke total score and Factor 1 score (0.24 points and 0.37 points, respectively) for the subjects who switched to THS 2.2



Menthol use compared to subjects who continued to smoke mCC, although 95% CIs for all parameters spanned 0.

The urge-to-smoke overall and factor scores of subjects who switched to THS 2.2 Menthol use were higher than that observed in subjects who abstained from smoking, with LS mean differences of 1.06 points (95% CI: 0.56, 1.55), 1.50 points (95% CI: 0.92, 2.07), and 0.63 points (95% CI: 0.16, 1.10) for QSU-brief total score, Factor 1 score, and Factor 2 score, respectively.

Analysis using the FAS showed consistent results to that of the PP Set, in respect to the 95% CI around 0.

11.3.4.2 MNWS-R During the Study

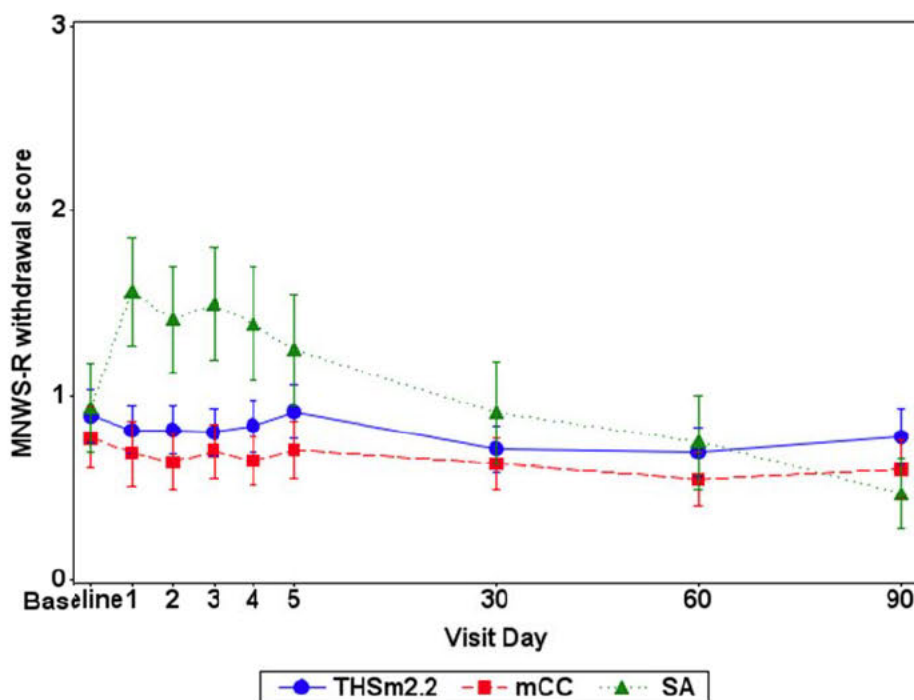
Responses to the MNWS questionnaire results are listed by subject in [Appendix 15, Listing 15.3.6.13](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.39.1](#) and [Table 15.2.4.39.2](#) for the PP Set and FAS, respectively.

Line graphs showing the arithmetic mean scores and 95% CIs for total score for the MNWS questionnaire over the course of the study are presented in [Appendix 15, Figure 15.1.2.8.1](#) and [Figure 15.1.2.8.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Figure 63](#).

The MNWS revised version (MNWS-R) is a valid and reliable scale of withdrawal. Subjects were asked to rate the items for the previous 24 hours on a scale ranging from 0 to 4 (where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe) and the total score was calculated by summing the results of the first 9 responses on the MNWS questionnaire.



Figure 63 Arithmetic Mean and 95% CI MNWS-R Total Score During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; MNWS = Minnesota nicotine withdrawal assessment - revised; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

MNWS-R total score reported a scale of 0 to 4. Higher scores indicate greater intensity of withdrawal symptoms.

Data Source: [Appendix 15, Figure 15.1.2.8.1](#)

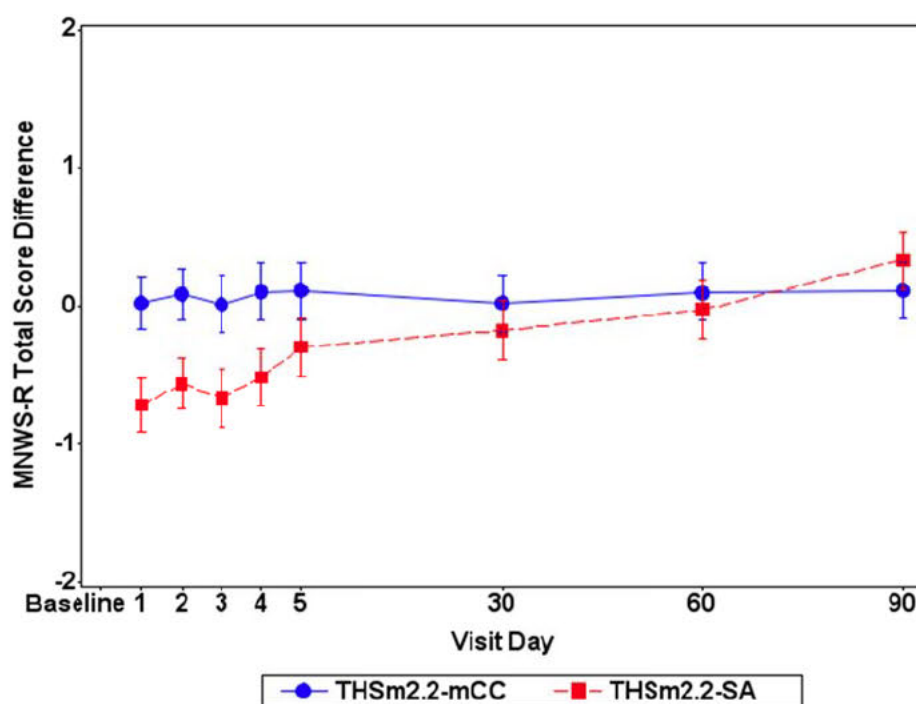
The mean MNWS-R withdrawal score values were 0.89 for the THS 2.2 Menthol arm, 0.77 for the mCC arm and 0.93 for the SA arm at baseline. For the THS 2.2 Menthol and mCC arms, the mean MNWS-R withdrawal score values remained stable over the 5 days of the Confinement Period (ranges of individual scores of 0.0 to 3.0 and 0.0 to 2.4, respectively). In the SA arm, the mean MNWS-R withdrawal score values increased from baseline to 1.56 on Day 1 (corresponding to a mean increase of 18.91%). The mean MNWS-R withdrawal score value was 1.25 on Day 5.

During the Ambulatory period, the mean MNWS-R withdrawal scores remained stable compared to baseline for the THS 2.2 Menthol and mCC arms, with Day 90 values of 0.77 and 0.60, respectively. In the SA arm, the MNWS-R withdrawal score was 0.47 at Day 90, corresponding to a decrease from baseline of -39.20%.



The results from the statistical analysis of the MNWS-R withdrawal score are tabulated in Table 121 and Table 122, and in Appendix 15, Table 15.1.2.4.40.1 and Table 15.1.2.4.40.2 for the PP Set and FAS, respectively. Profiles of the LS mean differences (THS 2.2 – mCC and THS 2.2 – SA) over time are presented in Appendix 15, Figure 15.1.2.9.1 and Figure 15.1.2.9.2 for the PP Set and FAS, respectively and data for the PP Set are provided in Figure 64.

Figure 64 Mean and 95% CI Total Scores Least Squares Means Differences for MNWS-R During the Course of the Study (PP Set)



Abbreviations: CI = confidence intervals; mCC = menthol conventional cigarettes; MNWS-R = Minnesota nicotine withdrawal scale – revised; PP = peer protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

MNWS-R total score was reported as a scale of 0 to 4. Higher scores indicate greater intensity of withdrawal symptoms.

Data Source: Appendix 15, Figure 15.1.2.9.1

The mean LS mean differences of THS 2.2 Menthol – mCC for MNWS-R total scores remained stable through the Confinement Period, with a difference of 0.02 on Day 1 and 0.11 on Day 5. The mean LS mean differences of THS 2.2 Menthol – SA for MNWS-R total scores was -0.72 on Day 1 and -0.30 on Day 5 (Figure 64).



During the Ambulatory Period, the mean LS mean differences of THS 2.2 Menthol – mCC for MNWS-R total scores remained stable, with a difference of 0.11 on Day 90. Whereas, the mean LS mean differences of THS 2.2 Menthol – SA for MNWS-R total scores were -0.18, -0.03, and 0.33 on Days 30, 60, and 90, respectively (Figure 64).

Table 121 Analysis of MNWS-R Questionnaire Scores on Day 5 (PP Set)

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Withdrawal score	Day 5	THS m2.2	75	0.90	0.11	-0.10, 0.31
		mCC	41	0.79		

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Withdrawal Score	Day 5	THS m2.2	75	0.90	-0.30	-0.51, -0.09
		SA	39	1.20		

Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; LS = least squares; MNWS-R = Minnesota nicotine withdrawal scale – revised; PP = per protocol; QSU-brief = questionnaire of smoking urges (brief version); SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.40.1](#).

On Day 5, there was no notable difference in MNWS-R total scores between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC with the 95% CI of the LS mean difference spanning 0.

On Day 5, the LS mean difference of the MWNS-R total score was higher for subjects who abstained from smoking compared to subjects who switched to THS 2.2 Menthol, with an LS mean difference of -0.30 (95% CI: -0.51, -0.09).

**Table 122 Analysis of MNWS-R Questionnaire Scores on Day 90 (PP Set)**

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Withdrawal score	Day 90	THS m2.2	69	0.76	0.11	-0.09, 0.30
		mCC	41	0.65		

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Withdrawal score	Day 90	THS m2.2	69	0.76	0.33	0.12, 0.53
		SA	37	0.44		

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarette; MNWS-R = Minnesota nicotine withdrawal scale – revised; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.40.1](#).

On Day 90, there was no notable difference in MNWS-R total scores between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with the 95% CI of the LS mean difference spanning 0.

On Day 90, the LS mean difference of the MWNS-R total score was higher for subjects who switched to THS 2.2 Menthol compared to subjects who abstained from smoking, with an LS mean difference of 0.33 (95% CI: 0.12, 0.53).

Analysis using the FAS showed consistent results to that of the PP Set.

11.3.4.3 Modified Cigarette Evaluation Questionnaire During the Study

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 15.3.6.14](#). The subscale scores for the MCEQ are summarized in [Appendix 15, Table 15.2.4.37.1](#) and [Table 15.2.4.37.2](#) for the PP Set and the FAS, respectively.

Line graphs showing the arithmetic mean and 95% CI for the individual subscales scores are presented for the PP Set and the FAS in [Figure 15.1.2.6.1](#) and [Figure 15.1.2.6.2](#), respectively.



For craving, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, decreases from baseline were observed as early as Day 1 in the THS 2.2 Menthol arm, ranging from -3.41% (95% CI: -16.41, 9.60) to -23.76% (95% CI: -30.33, -17.18); whereas changes from baseline observed in the mCC arm ranged from 10.78% (95% CI: -1.11, 22.67) to -3.32% (95% CI: -10.44, 3.81). For the aversion subscale, an increase from baseline was observed on Day 1 for the THS 2.2 Menthol (16.26%; 95% CI: 0.83, 31.69) and mCC (7.77%; 95% CI: -10.35, 25.90) study arms.

Least square means differences between the THS 2.2 and mCC arms and 95% CI for the individual subscales scores are presented for the PP Set and the FAS in [Figure 15.1.2.7.1](#) and [Figure 15.1.2.7.2](#), respectively. Data for the LS mean differences between the THS 2.2 Menthol and mCC arms for the PP Set is provided in [Table 123](#).

Table 123 The LS Mean of THS 2.2 Menthol – mCC Differences for MCEQ Subscales (PP Set)

Subscale	THS 2.2 Menthol - mCC							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 30	Day 60	Day 90
Aversion	0.07	-0.10	-0.08	-0.19	0.07	-0.03	-0.01	-0.16
Craving Reduction	-0.54	-0.56	-0.27	-0.50	-0.02	-0.11	0.13	-0.15
Enjoyment of Respiratory Tract Sensation	-0.56	-0.62	-0.20	-0.32	-0.13	0.14	0.19	0.30
Psychological Reward	-0.41	-0.35	-0.27	-0.24	-0.21	-0.14	0.04	0.00
Smoking Satisfaction	-0.86	-0.86	-0.54	-0.53	-0.39	-0.31	-0.21	0.01

Abbreviations: LS = least squares; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.
Data Source: [Appendix 15, Table 15.2.4.38.1](#).

On Day 1, the mean scores for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales were lower in subjects who switched to THS 2.2 Menthol use compared to those observed in subjects who continued to smoke mCC (THS m2.2 – mCC difference). Over the course of the study the LS mean differences between the THS 2.2 Menthol and mCC arms became less for the craving reduction, enjoyment of respiratory tract sensation, psychological reward,



and smoking satisfaction subscales, with LS mean differences on Day 5 of -0.02, -0.13, -0.21, and -0.39, respectively, and LS mean differences on Day 90 of -0.15, 0.30, 0.00, and 0.01, respectively. The LS mean differences for the aversion subscale were minimal compared to the other subscales.

The results from the statistical analysis of the MCEQ subscales score are presented in [Appendix 15](#), [Table 15.2.4.38.1](#) and [Table 15.2.4.38.2](#), and [Figures 15.1.2.7.1](#) and [15.1.2.7.2](#) for the PP Set and FAS, respectively. The results from the statistical analysis on the PP Set for each MCEQ subscale on Days 5 and 90 are tabulated in [Table 124](#) and [Table 125](#).

Table 124 Analysis of MCEQ Subscales on Day 5 (PP Set)

Subscale	Time Point	Product Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Aversion	Day 5	THS m2.2	75	1.56	0.07	-0.23, 0.37
		mCC	41	1.49		
Craving reduction	Day 5	THS m2.2	75	3.63	-0.02	-0.55, 0.50
		mCC	41	3.66		
Enjoyment of respiratory tract sensation	Day 5	THS m2.2	75	3.26	-0.13	-0.55, 0.29
		mCC	41	3.39		
Psychological reward	Day 5	THS m2.2	75	2.72	-0.21	-0.51, 0.10
		mCC	41	2.93		
Smoking satisfaction	Day 5	THS m2.2	75	3.51	-0.39	-0.81, 0.03
		mCC	41	3.89		

Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; LS = least squares; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, mCC consumption reported at Screening as fixed effect factors

Data Source: [Appendix 15](#), [Table 15.2.4.38.1](#).

On Day 5, there were no notable differences observed for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC for aversion, craving reduction, enjoyment of respiratory tract sensation subscales, with all 95% CIs of the LS mean difference spanning 0. For psychological reward and smoking satisfaction, the LS means in subjects who switched to THS 2.2 Menthol use were 0.21 and 0.39 lower



than that observed in subjects who continued to smoke mCC (95% CI: -0.51, 0.10; -0.81, 0.03; respectively).

Table 125 Analysis of MCEQ Subscales on Day 90 (PP Set)

Subscale	Time Point	Product Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Aversion	Day 90	THS m2.2	69	1.57	-0.16	-0.49, 0.18
		mCC	41	1.72		
Craving reduction	Day 90	THS m2.2	69	4.08	-0.15	-0.62, 0.32
		mCC	41	4.22		
Enjoyment of respiratory tract sensation	Day 90	THS m2.2	69	3.77	0.30	-0.18, 0.78
		mCC	41	3.47		
Psychological reward	Day 90	THS m2.2	69	3.01	0.00	-0.37, 0.36
		mCC	41	3.01		
Smoking satisfaction	Day 90	THS m2.2	69	3.89	0.01	-0.39, 0.41
		mCC	41	3.89		

Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; LS = least squares; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from a mixed model conducted on log-transformed values with log-transformed baseline value, study arm, sex, mCC consumption reported at Screening as fixed effect factors

Data Source: [Appendix 15, Table 15.2.4.38.1](#).

On Day 90, following the Ambulatory Period, there was no notable difference observed for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, for the aversion, craving reduction, psychological reward, smoking satisfaction subscales, with all 95% CIs spanning 0. For enjoyment of respiratory tract sensation, the LS means in subjects who switched to THS 2.2 Menthol use were 0.30 higher than that observed in subjects who abstained from smoking (95% CI: -0.18, 0.78).

Analysis using the FAS showed consistent results to that of the PP Set.



11.3.5 Human Smoking Topography During the Study

11.3.5.1 Human Smoking Topography Questionnaire

Responses to the HST questionnaire are listed in [Appendix 15, Listing 15.3.7.2](#) and are summarized by product use in [Appendix 15, Table 15.2.4.41](#) for the PP Set.

11.3.5.2 Human Smoking Topography Device

The individual parameters collected from the HST SODIM[®] device and changes from baseline are listed in [Appendix 15, Listing 15.3.7.1](#) and are summarized by product use in [Appendix 15, Table 15.2.4.42](#) for the PP Set.

Line graphs of arithmetic mean and 95% CIs are presented for each HST parameter in the THS 2.2 Menthol and mCC arms for the overall study for the PP Set in [Appendix 15, Figure 15.1.2.10](#).

The results of the statistical analysis of the HST per-cigarette parameters are tabulated in [Appendix 15, Table 15.2.4.43](#) and [Table 126](#) and [Table 127](#) for Days 1 and 4; and Day 90, respectively.

[Appendix 15, Figure 15.1.2.10](#) showed that the baseline values for each assessed parameter were generally comparable between the THS 2.2 Menthol and the mCC arms.

On Day 1, rapid decreases from baseline were observed in the THS 2.2 Menthol arm for average flow, average peak flow, total work, average work, smoking intensity, total puff volume, average puff volume, total inter puff interval, average inter puff interval, and total smoking duration. By Day 4, average flow, average peak flow, total work, average work, smoking intensity, total puff volume, and average puff volume had increased from Day 1. Whereas, total inter puff interval, average inter puff interval, and total smoking duration had continued to decrease from Day 1.

In contrast, average pressure drop, average peak pressure drop, puff time index, average puff duration, total puff duration, and puff frequency of the THS 2.2 Menthol arm increased from baseline on Day 1 and either continued to increase or remained stable on Day 4. Total number of puffs increased slightly from baseline on Day 1 and then decreased to approximately baseline levels by Day 4.

In the mCC arm, average peak flow, average flow, total puff volume, average work, average pressure drop, average peak pressure drop, and total work had decreases from baseline. Total number of puffs and total puff duration had a similar mCC profile during the Confinement Period to the THS 2.2 Menthol arm, with an initial increase and then decrease to Day 4. In the case of total puff duration, the magnitude of the change was



lower than for the THS 2.2 Menthol arm. All of the other HST parameters remained at approximate baseline levels through the Confinement Period.

Appendix 15, Figure 15.1.2.10 shows that during the Ambulatory Period, total inter puff interval, average inter puff interval, and total smoking duration remained decreased from baseline to Day 30. Total smoking duration gradually increased from Day 30 to Day 90. Total smoking duration remained on Day 30 levels from Days 30, 60, and 90. Inter puff interval continued to decrease from baseline from Day 30 to Day 90.

Of those parameters that decreased on Day 1 but had begun to return to baseline on Day 4, total puff volume and average puff volume remained at approximately the Day 4 level through the rest of the study to Day 90, although, total puff volume did fluctuate between Days 30, 60 and 90. Average flow and average peak flow continued to increase from Day 4 to Day 30 and then remained stable until Day 90. Total work and average work also continued to increase from Day 4, until Day 60, where these HST parameters were now above baseline levels. Smoking intensity which had returned to baseline levels on Day 4, gradually increased from baseline to Day 60, where it plateaued until Day 90.

Of those parameters that increased during the Confinement Period, total number of puffs, which had returned to baseline on Day 4, continued to decrease to Day 30 and then increased to Day 90. Average puff duration and total puff duration, which had remained stable on Day 4 from the increase on Day 1, decreased slightly to Day 30 and then increased again on Day 60. Average pressure drop, average peak pressure drop, puff time index, and puff frequency, which had all increased from baseline on Days 1 and 4 in the Confinement Period, continued to increase through to Day 90.

In the mCC arm, total number of puffs and total puff duration had a similar profile to the THS 2.2 Menthol arm, but at a lower overall magnitude (including baseline). Average puff volume, average puff duration, average pressure drop, and average peak pressure drop had remained at approximate baseline levels on Days 1 and 4, and continued to do so during the Ambulatory Period as well. Puffing time index, puffing frequency, and smoking intensity also remained at baseline levels through to Day 30 and then had an increase from baseline on Day 60. Average flow, average peak glow, total work, and average work had all had an initial small decrease from baseline in the Confinement Period, and remained stable at this decreased level during the Ambulatory Period.

Lastly, total inter puff interval, average inter puff interval, and total smoking duration had continued to remain stable from Day 4, but decreased to Day 30 where total inter puff interval and total smoking duration plateaued until Day 90, and average inter puff interval increased on Day 60. Total work, which remained stable from Day 4, also had a drop during the Ambulatory Period on Day 60.



Table 126 Analysis of HST Parameters per-Cigarette During the Confinement Period (Averaged over Visit) (PP Set)

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference	95% CI
Total puff volume (mL)	Day 1	THS m2.2	50	723.39	-115.87	-233.83, 2.09
		mCC	28	839.26		
	Day 4	THS m2.2	49	758.25	-35.82	-170.54, 98.90
		mCC	25	794.07		
Average puff volume (mL)	Day 1	THS m2.2	50	41.27	-8.32	-13.84, -2.79
		mCC	28	49.58		
	Day 4	THS m2.2	49	45.42	-3.05	-9.45, 3.35
		mCC	25	48.47		
Average puff duration (s)	Day 1	THS m2.2	50	1.89	0.19	0.01, 0.38
		mCC	28	1.69		
	Day 4	THS m2.2	49	1.94	0.30	0.13, 0.47
		mCC	25	1.64		
Total puff duration (s)	Day 1	THS m2.2	50	33.40	4.06	-0.71, 8.82
		mCC	28	29.34		
	Day 4	THS m2.2	49	32.45	4.92	0.29, 9.55
		mCC	25	27.53		
Average flow (mL/s)	Day 1	THS m2.2	50	24.20	-7.04	-9.39, -4.70
		mCC	28	31.24		
	Day 4	THS m2.2	49	25.39	-5.69	-8.88, -2.51
		mCC	25	31.08		
Average peak flow (mL/s)	Day 1	THS m2.2	50	37.09	-10.71	-14.45, -6.98
		mCC	28	47.81		
	Day 4	THS m2.2	49	39.04	-7.80	-12.66, -2.95
		mCC	25	46.84		



Table 126 Analysis of HST Parameters per-Cigarette During the Confinement Period (Averaged over Visit) (PP Set) Continued

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference	95% CI
Puff frequency (puffs/min)	Day 1	THS m2.2	50	5.32	0.32	-0.08, 0.72
		mCC	28	5.00		
	Day 4	THS m2.2	49	5.37	0.22	-0.28, 0.73
		mCC	25	5.14		
Total number of puffs	Day 1	THS m2.2	50	19.05	0.87	-1.52, 3.26
		mCC	28	18.17		
	Day 4	THS m2.2	49	17.61	0.43	-1.70, 2.57
		mCC	25	17.17		
Total inter puff interval (s)	Day 1	THS m2.2	50	201.17	-5.87	-29.29, 17.55
		mCC	28	207.04		
	Day 4	THS m2.2	49	181.64	-24.56	-54.93, 5.82
		mCC	25	206.20		
Average inter puff interval (s)	Day 1	THS m2.2	50	11.58	-1.07	-2.49, 0.36
		mCC	28	12.64		
	Day 4	THS m2.2	49	10.82	-1.91	-3.51, -0.31
		mCC	25	12.73		
Total smoking duration (s)	Day 1	THS m2.2	50	235.24	-2.47	-27.44, 22.51
		mCC	28	237.70		
	Day 4	THS m2.2	49	214.85	-19.63	-51.28, 12.03
		mCC	25	234.48		
Total work (mJ)	Day 1	THS m2.2	50	1968.73	-163.40	-560.17, 233.37
		mCC	28	2132.13		
	Day 4	THS m2.2	49	2031.40	35.79	-395.68, 467.26
		mCC	25	1995.61		
Average work (mJ)	Day 1	THS m2.2	50	118.64	-10.30	-29.14, 8.53
		mCC	28	128.95		
	Day 4	THS m2.2	49	126.47	1.64	-22.28, 25.55
		mCC	25	124.83		



Table 126 Analysis of HST Parameters per-Cigarette During the Confinement Period (Averaged over Visit) (PP Set) Continued

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference	95% CI
Average pressure drop (mmWg)	Day 1	THS m2.2	50	237.80	30.37	9.76, 50.98
		mCC	28	207.43		
	Day 4	THS m2.2	49	243.27	28.15	6.02, 50.27
		mCC	25	215.13		
Average peak pressure drop (mmWg)	Day 1	THS m2.2	50	388.24	44.83	13.17, 76.49
		mCC	28	343.41		
	Day 4	THS m2.2	49	397.23	49.63	13.56, 85.70
		mCC	25	347.60		
Smoking intensity (mL/s)	Day 1	THS m2.2	50	3.58	-0.33	-0.91, 0.25
		mCC	28	3.91		
	Day 4	THS m2.2	49	3.93	-0.17	-0.92, 0.59
		mCC	25	4.10		
Puffing time index (%)	Day 1	THS m2.2	50	16.07	2.48	0.70, 4.27
		mCC	28	13.58		
	Day 4	THS m2.2	49	16.93	2.78	0.89, 4.67
		mCC	25	14.15		

Abbreviations: ANCOVA = analysis of covariance; mCC = Menthol conventional cigarette; CI = confidence interval; HST = human smoking topography; LS = least squares; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.43](#).

No notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC were observed in total number of puffs, total puff volume, total inter puff interval, smoking intensity, puffing frequency, average work, total smoking duration, and total work on both Days 1 and 4, with 95% CIs for each assessment spanning 0.

Average peak pressure drop (44.83 mmWg [13.17, 76.49] and 49.63 mmWg [13.56, 85.70], respectively), average pressure drop (30.37 mmWg [9.76, 50.98] and 28.15 mmWg [6.02, 50.27], respectively), average puff duration (0.19 s [0.01, 0.38] and



0.30 s [0.13, 0.47], respectively), and puffing time index (2.48% [0.70, 4.27] and 2.87% [0.89, 4.67], respectively) were increased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on Days 1 and 4. In addition, total puff duration (4.92 s [0.29, 9.55]) was increased on Day 4.

Average flow (-7.04 mL/s [-9.39, -4.70] and -5.69 mL/s [-8.88, -2.51], respectively) and average peak flow mL/s (-10.71 [-14.45, -6.98] and -7.80 mL/s [-12.66, -2.95], respectively) were notably decreased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on Days 1 and 4. In addition, average puff volume (-8.32 mL [-13.84, -2.79]) was decreased notably on Day 1 and average inter puff interval (-1.91 s [-3.51, -0.31]) was decreased on Day 4.

**Table 127 Analysis of HST Parameters per-Cigarette During the Ambulatory Period (Averaged over Visit) (PP Set)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference	95% CI
Total puff volume (mL)	Day 90	THS m2.2	43	729.85	-23.47	-141.54, 94.61
		mCC	25	753.32		
Average puff volume (mL)	Day 90	THS m2.2	43	41.49	-9.67	-15.87, -3.48
		mCC	25	51.17		
Average puff duration (s)	Day 90	THS m2.2	43	1.90	0.26	-0.02, 0.54
		mCC	25	1.64		
Total puff duration (s)	Day 90	THS m2.2	43	34.06	10.12	3.31, 16.92
		mCC	25	23.94		
Average flow (mL/s)	Day 90	THS m2.2	43	25.35	-8.46	-11.94, -4.98
		mCC	25	33.82		
Average peak flow (mL/s)	Day 90	THS m2.2	43	38.36	-13.09	-18.85, -7.32
		mCC	25	51.45		
Puff frequency (puffs/min)	Day 90	THS m2.2	43	6.20	1.03	0.11, 1.94
		mCC	25	5.18		
Total inter puff interval (s)	Day 90	THS m2.2	43	168.55	-12.50	-45.24, 20.24
		mCC	25	181.05		
Average inter puff interval (s)	Day 90	THS m2.2	43	9.75	-3.00	-5.25, -0.74
		mCC	25	12.74		



Table 127 Analysis of HST Parameters per-Cigarette During the Ambulatory Period (Averaged over Visit) (PP Set) Continued

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference	95% CI
Total smoking duration (s)	Day 90	THS m2.2	43	202.93	-1.84	-35.93, 32.24
		mCC	25	204.77		
Total number of puffs	Day 90	THS m2.2	43	18.57	3.19	0.49, 5.89
		mCC	25	15.37		
Total work (mJ)	Day 90	THS m2.2	43	2715.79	798.00	326.36, 1269.64
		mCC	25	1917.80		
Average work (mJ)	Day 90	THS m2.2	43	157.20	22.69	-0.97, 46.34
		mCC	25	134.51		
Average pressure drop (mmWg)	Day 90	THS m2.2	43	331.29	113.00	68.47, 157.53
		mCC	25	218.29		
Average peak pressure drop (mmWg)	Day 90	THS m2.2	43	527.93	165.50	108.69, 222.31
		mCC	25	362.43		
Smoking intensity (mL/s)	Day 90	THS m2.2	43	4.32	-0.04	-0.98, 0.91
		mCC	25	4.36		
Puffing time index (%)	Day 90	THS m2.2	43	18.92	5.37	2.20, 8.54
		mCC	25	13.55		

Abbreviations: ANCOVA = analysis of covariance; HST = human smoking topography; mCC = Menthol conventional cigarette; CI = confidence interval; LS = least squares; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted LS means and CIs from an ANCOVA model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors

Data Source: [Appendix 15, Table 15.2.4.43](#).

No notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC were observed in total puff volume, average puff duration, total inter puff interval, total smoking duration, average work, and smoking intensity at the end of the Ambulatory Period (Day 90), with 95% CIs for each assessment spanning 0.



Puffing time index, puff frequency, average pressure drop, average peak pressure drop, total work, total puff duration, and total number of puffs were notably increased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on Day 90.

Average inter puff interval, average peak flow, average flow, and average puff volume were notably decreased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on Day 90.

An additional posthoc analysis on the PP Set was conducted to facilitate comparison of this data with other studies.

The individual parameters collected from the HST SODIM[®] device and changes from baseline are listed in [Appendix 15, Listing 15.3.7.1](#) and are summarized by product use in [Appendix 15, Table 15.2.4.42.1](#) for the PP Set.

Line graphs of geometric mean and 95% CIs are presented for each HST parameter in the THS 2.2 Menthol and mCC arms for the overall study for the PP Set in [Appendix 15, Figure 15.1.2.10.1](#).

The results of the statistical analysis of the HST per-cigarette parameters are tabulated in [Appendix 15, Table 15.2.4.43.1](#).

The posthoc analysis showed that the results for each assessed parameter were generally comparable with the original analyses.

11.3.6 Visual Inspection of the THS Tobacco Plugs

Results from the inspection of individual tobacco plugs are listed in [Appendix 15, Listing 15.3.6.17](#) and are summarized in [Appendix 15, Table 15.2.4.47](#) and [Table 128](#) and [Table 129](#).

**Table 128 Summary of Visual Inspection of the THS m2.2 Tobacco Plug (FAS) During the Confinement Period**

Evaluation	THS m2.2 (N=78)				
	Day 1 n = 887	Day 2 n = 923	Day 3 n = 936	Day 4 n = 947	Day 5 n = 1069
0	828 (93.3%)	899 (97.4%)	918 (98.1%)	926 (97.8%)	1045 (97.8%)
1	5 (0.6%)	10 (1.1%)	13 (1.4%)	7 (0.7%)	13 (1.2%)
2	1 (0.1%)	-	-	-	-
Missing	53 (6.0%)	14 (1.5%)	5 (0.5%)	14 (1.5%)	11 (1.0%)

Abbreviations: FAS = Full Analysis Set; n = number of THS 2.2 products used; N = number of subjects;
THS m2.2 = Tobacco Heating System 2.2 Menthol.

Percentages based on the number of THS m2.2 products used

0 = no overheating, 1 = white spot(s) inside the tobacco plug, 2 = ashes inside the tobacco plug and burnt paper.

Data Source: [Appendix 15, Table 15.2.4.47](#).

Visual inspection of THS Tobacco Plugs was possible for the majority of plugs on Days 1 to 5, for an average of approximately 950 plugs per day. On all study days, the majority of THS Tobacco Plugs ($\geq 93.3\%$ each day) showed no overheating (grade 0). The proportion of THS Tobacco Plugs with white spot(s) inside the tobacco plug (grade 1) was similar across all study days (range 0.6% to 1.4%). There was only 1 occurrence showing ashes inside the tobacco plug and burnt paper (grade 2) following visual inspection among more than 4500 THS Tobacco Plugs analyzed.

Table 129 Summary of Visual Inspection of the THS Tobacco Plug (FAS) During the Ambulatory Period

Evaluation	THS m2.2 (N=78)		
	Day 30 n = 686	Day 60 n = 711	Day 90 n = 804
0	678 (98.8%)	698 (98.2%)	795 (98.9%)
1	4 (0.6%)	8 (1.1%)	5 (0.6%)
Missing	4 (0.6%)	5 (0.7%)	4 (0.5%)

Abbreviations: FAS = Full Analysis Set; n = number of THS 2.2 products used; N = number of subjects;
THS m2.2 = Tobacco Heating System 2.2 Menthol.

Percentages based on the number of non-missing inspections.

0 = no overheating, 1 = white spot(s) inside the tobacco plug, 2 = ashes inside the tobacco plug and burnt paper.

Data Source: [Appendix 15, Table 15.2.4.47](#).

Visual inspection of THS Menthol Tobacco Plugs was possible for the majority of plugs on Days 30, 60, and 90 ($>99.3\%$ each day; approximately 729 plugs per day). On all



study days, the majority of THS Menthol Tobacco Plugs showed no overheating (grade 0). The proportion of THS Menthol Tobacco Plugs with white spot(s) inside the tobacco plug (grade 1) was similar across all study days (range 0.6% to 1.2%). There was no occurrence of THS Menthol Tobacco Plugs showing ashes inside the tobacco plug and burnt paper (grade 2).

11.3.6.1 Filter Analysis

Results from the filter analysis are listed in [Appendix 15, Listing 15.3.6.18](#), and are summarized in [Appendix 15, Table 15.2.4.48](#).

Overall, 78 subjects in the THS 2.2 Menthol arm had the mouthpiece analyzed. The mean values for all THS Tobacco plug filter analysis parameters assessed, nicotine amount, absolute UV TAR absorbance and normalized UV absorbance appeared to increase slightly between Day 1 and Day 5.



11.4 Statistical and Analytical Issues

11.4.1 Multicenter Studies

This was originally to be a two-site study; however, 1 of the sites was terminated due to ICH/GCP non-compliance. In total 219 smokers were randomized, so that the target sample size of 160 smokers would be recruited at a single site, the Tokyo Heart Center.

11.4.2 Sample Size

Originally it was planned that a total of 160 smokers would be randomized over 2 sites. However, due to the site that terminated due to ICH/GCP non-compliance 219 smokers were randomized, so that the 160 smokers were recruited at the Tokyo Heart Center, to demonstrate a reduction of at least 50% on all 5 BoExp analysis for primary endpoints in smokers switching from mCC to THS 2.2 Menthol as compared to those continuing to smoke mCC, using one-sided test with 2.5% type I error probability (see [Section 9.7.4](#) for details relating to the determination of the sample size).

11.4.3 Adjustment for Covariates

For all analyses the stratification factors of sex and mCC consumption (average daily mCC consumption over the last 4 weeks as reported during Screening) were included in the model and a baseline endpoint value was included, except for the analysis of the PK parameters of nicotine and cotinine.

11.4.4 Handling of Dropouts or Missing Data

As per the SAP ([Appendix 16.1.8](#)), the following rules were followed for endpoint analyses:

For laboratory parameters, lower limit of quantification (LLOQ) values were imputed using LLOQ/2. For values above the upper limit of quantification (ULOQ), the ULOQ were imputed. The number of values below LLOQ or above ULOQ were presented in each summary table. If 50% or more data values were below LLOQ or above ULOQ, only the number (%) of values below LLOQ or above ULOQ were reported in the summaries, together with minimum and maximum of the observed values. Missing data at baseline were not imputed.

For analysis of BoExp and CREs:

- A LOCF approach was implemented to replace all missing data with the last available data for each parameter being assessed



- For parameters assessed at several time points during a visit, the last available data at the time point being assessed collected at the previous study visit were used in the analyses.

For daily product use data in safety summaries, product use categories were defined based on percentage of THS 2.2 Menthol use calculated by averaging non-missing consumption data over the entire Ambulatory time interval.

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

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

For the MNWS, QSU-brief, and MCEQ questionnaire data, total scores and factors or subscale scores were derived by averaging the individual non-missing item scores if at least 50% were non-missing, otherwise they were set to missing.

For missing or partial dates, and missing data, see the SAP ([Appendix 16.1.8](#)) for more details.

11.4.5 Interim Analysis and Data Analysis

No interim analysis was planned or conducted for this study.

11.4.6 Multiple Comparison/Multiplicity

The primary endpoints were tested using a multiple testing procedure to preserve the overall alpha level by simultaneously testing the endpoints using a closed procedure with



each test performed at an alpha level of 1-sided 2.5%. This implied that statistical significance was required for all primary endpoints in order to be able to make confirmatory claims about any of the endpoints.

No adjustment was made on any of the secondary endpoints.

11.4.7 Active Control Studies Intended to Show Equivalence

Not applicable for this study.

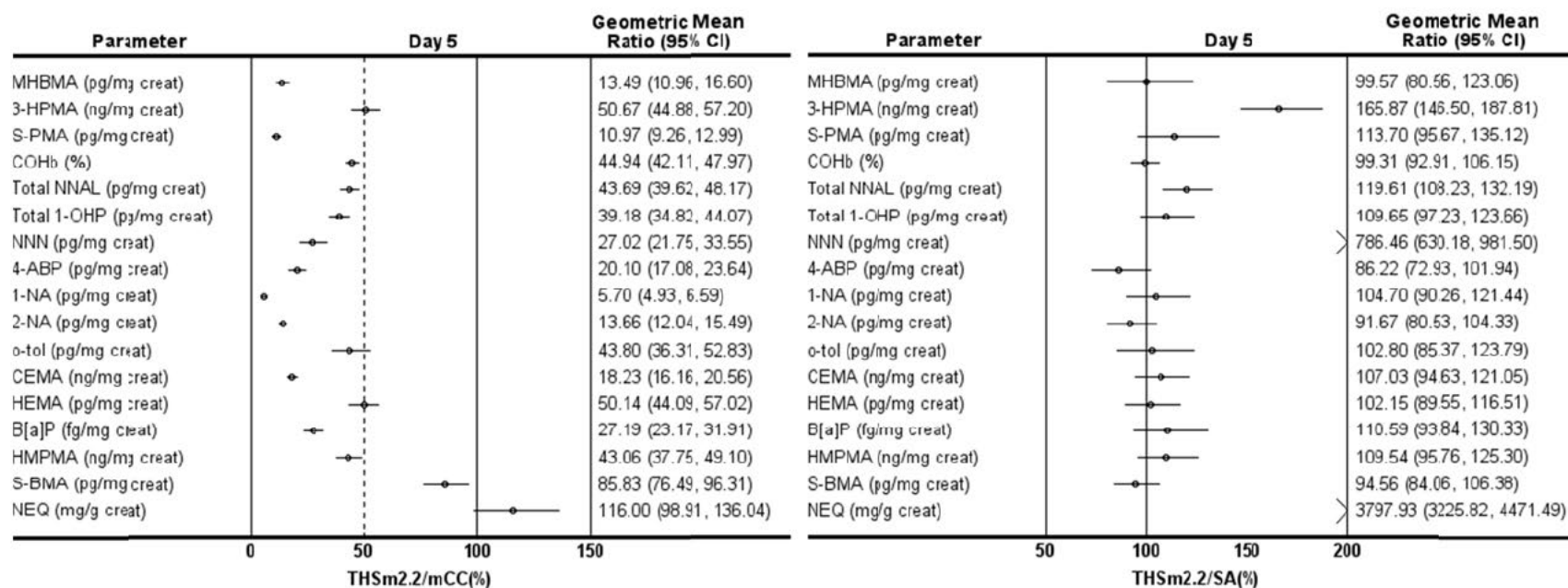
11.4.8 Examination of Sub-groups

Results for the exploratory sub-groups are discussed in the appropriate sections along with the main analyses.

11.5 Conclusions

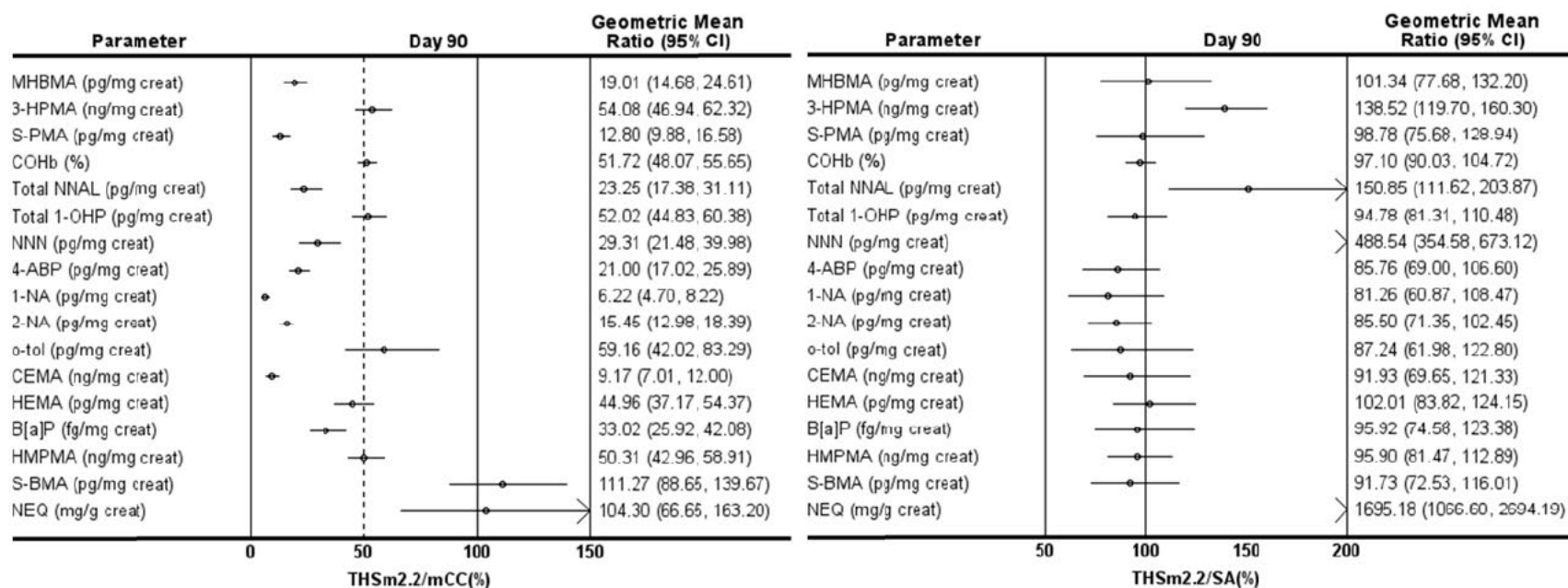
11.5.1 Summary of Statistical Analysis During the Study

A graphical summary of statistical analysis for all biomarkers of exposure adjusted for creatinine for the THS 2.2 Menthol arm versus mCC, or SA on Day 5 during the Confinement Period and on Day 90 following the Ambulatory Period is presented in [Figure 65](#) and [Figure 66](#), respectively.

**Figure 65 Forest Plot of Statistical Analysis of Biomarker s of Exposure on Day 5 versus mCC or SA – PP Set**

Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; mCC = menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NEQ = nicotine equivalents; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; NNN = N-nitrososnoronicotine; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.1.1](#)

**Figure 66 Forest Plot of Statistical Analysis of Biomarkers of Exposure on Day 90 versus mCC or SA – PP Set**

Abbreviations: Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; mCC = menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NEQ = nicotine equivalents; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; NNN = N-nitrososonornicotine; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; S-PMA = S-p-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.1.1](#)



11.5.2 Conclusions of the Study

Primary Objectives and Endpoints Analyses

The primary objectives for this study assessed on Day 5 for the BoExp COHb in blood (expressed as % saturation of hemoglobin); and for the following BoExp expressed as urinary concentration adjusted for creatinine in urine: MHBMA (pg/mg creat); 3-HPMA (ng/mg creat); and S-PMA (pg/mg creat); and on Day 90 Total NNAL expressed as urinary concentration adjusted for creatinine in urine (pg/mg creat).

Reductions were observed in the level of each BoExp assessed for the THS 2.2 Menthol arm compared to the mCC arm on Day 5, with reductions of 55% (95% CI: 52.0, 57.9) in COHb, 87% (95% CI: 83.4, 89.0) in MHBMA, 49% (95% CI: 42.8, 55.1) in 3-HPMA, and 89% (95% CI: 87.0, 90.7) in S-PMA. In addition, on Day 90, a reduction of 77% (95% CI: 68.9, 82.6) was observed in the level of Total NNAL.

For all of the BoExp included in the analysis of the primary objective at their respective time points, the study showed a reduction in smokers that switch to THS 2.2 Menthol compared to smokers that continued to smoke mCC. This reduction was 50% or more for COHb, MHBMA, Total NNAL, and S-PMA. A 49% reduction was observed in 3-HPMA while achieving levels consistent with the expected effect compared to SA.

Secondary Objectives and Endpoints Analyses

Carboxyhemoglobin in Whole Blood, 3-HPMA, MHBMA, S-PMA, and Total NNAL (Concentrations Adjusted for Creatinine) versus Smoking Abstinence and Menthol Conventional Cigarettes on Day 5 (Confinement Period) and on Day 90 (Ambulatory Period)

Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 and on Day 90 versus mCC and versus SA (PP Set)				
Biomarker/ Time point	Ratio THS m2.2:mCC		Ratio THS m2.2:SA	
	%	95% CI	%	95% CI
Evening COHb (%)				
Day 5	44.94	42.11, 47.97	99.31	92.91, 106.15
Day 90	51.72	48.07, 55.65	97.10	90.03, 104.72
Urinary MHBMA (pg/mg creat)				
Day 5	13.49	10.96, 16.60	99.57	80.56, 123.06
Day 90	19.01	14.68, 24.61	101.34	77.68, 132.20
Urinary 3-HPMA (ng/mg creat)				
Day 5	50.67	44.88, 57.20	165.87	146.50, 187.81
Day 90	54.08	46.94, 62.32	138.52	119.70, 160.30
Urinary S-PMA (pg/mg creat)				



Day 5	10.97	9.26, 12.99	113.70	95.67, 135.12
Day 90	12.80	9.88, 16.58	98.78	75.68, 128.94
Urinary Total NNAL (pg/mg creat)				
Day 5	43.69	39.62, 48.17	119.61	108.23, 132.19
Day 90	23.25	17.38, 31.11	150.85	111.62, 203.87
Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; mCC = menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.				

The reductions in COHb, 3-HPMA, MHBMA, and S-PMA observed on Day 5 during the Confinement Period for the THS 2.2 Menthol arm compared to the mCC arm were sustained during the Ambulatory Period, with decreases of 48% in COHb, 81% in MHBMA, 46% in 3-HPMA, and 87% in S-PMA, evident on Day 90. In addition, the reductions observed on Day 90 for Total NNAL were apparent on Day 5, with levels reduced by 56% in the THS 2.2 Menthol arm compared to the mCC arm.

There were no notable differences observed on Day 5 or Day 90 between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking for COHb, MHBMA, and S-PMA.

The levels of 3-HPMA and Total NNAL were higher for the THS 2.2 Menthol arm compared to the SA arm; 66% higher on Day 5 and 39% higher on Day 90 for 3-HPMA; and 20% higher on Day 5 and 51% higher on Day 90 for Total NNAL. Although, the numerical difference between the THS 2.2 Menthol and SA arms appeared substantial; when in the context of the reduction from mCC, THS 2.2 Menthol preserved most of the effect observed in the SA arm.

Other Biomarkers of Exposure (Exhaled CO [ppm] and Other Urinary Biomarkers of Exposure [Concentration Adjusted for Creatinine]) versus Menthol Conventional Cigarettes and Smoking Abstinence in the Confinement Period and Ambulatory Period

Analysis of Other Biomarkers of Exposure on Day 5 and on Day 90 versus mCC and versus SA (PP Set)				
Biomarker/ Time point	Ratio THS m2.2:mCC		Ratio THS m2.2:SA	
	%	95% CI	%	95% CI
Urinary Total 1-OHP (pg/mg creat)				
Day 5	39.18	34.82, 44.07	109.65	97.23, 123.66
Day 90	52.02	44.83, 60.38	94.78	81.31, 110.48
Urinary Total NNN (pg/mg creat)				
Day 5	27.02	21.75, 33.55	786.46	630.18, 981.50
Day 90	29.31	21.48, 39.98	488.54	354.58, 673.12
Urinary 4-ABP (pg/mg creat)				
Day 5	20.10	17.08, 23.64	86.22	72.93, 101.94



Day 90	21.00	17.02, 25.89	85.76	69.00, 106.60
Urinary 1-NA (pg/mg creat)				
Day 5	5.70	4.93, 6.59	104.70	90.26, 121.44
Day 90	6.22	4.70, 8.22	81.26	60.87, 108.47
Urinary 2-NA (pg/mg creat)				
Day 5	13.66	12.04, 15.49	91.67	80.53, 104.33
Day 90	15.45	12.98, 18.39	85.50	71.35, 102.45
Urinary o-tol (pg/mg creat)				
Day 5	43.80	36.31, 52.83	102.80	85.37, 123.79
Day 90	59.16	42.02, 83.29	87.24	61.98, 122.80
Urinary CEMA (ng/mg creat)				
Day 5	18.23	16.16, 20.56	107.03	94.63, 121.05
Day 90	9.17	7.01, 12.00	91.93	69.65, 121.33
Urinary HEMA (pg/mg creat)				
Day 5	50.14	44.09, 57.02	102.15	89.55, 116.51
Day 90	44.96	37.17, 54.37	102.01	83.82, 124.15
Urinary B[a]P (fg/mg creat)				
Day 5	27.19	23.17, 31.91	110.59	93.84, 130.33
Day 90	33.02	25.92, 42.08	95.92	74.58, 123.38
Urinary HMPMA (ng/mg creat)				
Day 5	43.06	37.75, 49.10	109.54	95.76, 125.30
Day 90	50.31	42.96, 58.91	95.90	81.47, 112.89
Urinary S-BMA (pg/mg creat)				
Day 5	85.83	76.49, 96.31	94.56	84.06, 106.38
Day 90	111.27	88.65, 139.67	91.73	72.53, 116.01
Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 4-ABP = 4-aminobiphenyl; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CO = carbon monoxide; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = menthol conventional cigarettes; NNN = N-nitrosonornicotine; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol				
Note: The difference in exhaled CO was calculated for THS 2.2 Menthol versus mCC or SA rather than the geometric LS mean ratio: Day 5 -13.10 (-14.70, -11.50) versus mCC and -0.85 (-2.49, 0.79) versus SA; Day 90 -9.28 (-10.75, -7.81) versus mCC and -0.23 (-1.75, 1.29) versus SA.				

Reductions observed in the THS 2.2 Menthol arm compared to the mCC arm (excluding S-BMA) ranged from 41% for o-toluidine to 94% for 1-NA.

Levels of the BoExp observed in subjects who switched to THS 2.2 Menthol use approached levels measured in subjects who abstained from smoking, except for Total NNN, which was 8-fold and 5-fold higher in the THS 2.2 Menthol arm compared to the SA arm on Day 5 and Day 90, respectively. Although, the numerical difference between the THS 2.2 Menthol and SA arms appeared substantial, when analyzed in the context of



the reduction from mCC, THS 2.2 Menthol preserved most of the effect observed in the SA arm.

Levels of S-BMA at Day 90 were comparable between subjects who switched to THS 2.2 Menthol use, subjects who continued smoking mCC, and subjects who abstained from smoking; and throughout the study S-BMA appeared to be unsuitable to discriminate between smokers and non-smokers.

Exposure to Nicotine (Concentrations and Pharmacokinetic Profiles) in Confinement Period and in Ambulatory Period

The NEQ urinary concentration adjusted for creatinine in the THS 2.2 Menthol arm initially decreased at Day 1 compared to baseline (-6.26%) and then increased from Day 1 to Day 5. On Day 5, NEQ urinary concentration adjusted for creatinine was approximately 16% (95% CI: -1.1, 36.0) higher in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC. This difference progressively reduced over time and on Day 90 the NEQ was comparable between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC (104%; 95% CI: 66.7, 163.2).

A similar trend was observed for nicotine and cotinine concentrations in plasma. On Day 5, the levels of nicotine and cotinine between 08:00 PM and 09:30 PM were 10% and 12% higher, respectively, in the THS 2.2 Menthol arm compared to the mCC arm (95% CI: -7.9, 32.3 for nicotine; and 95% CI: -0.13, 24.8 for cotinine). These differences decreased over time, starting from Day 60. There were no notable differences in evening plasma nicotine or cotinine levels in the THS 2.2 Menthol arm compared to the mCC arm on Day 90 (nicotine: 103%; 95% CI: 82.7, 129.3; cotinine: 106%; 95% CI: 89.9, 124.8). For the nicotine PK profile on Day 5, peak plasma concentrations were 31% (95% CI: 6.9, 59.6; 20.70 ng/mL for THS 2.2 Menthol arm and 15.67 ng/mL for mCC arm) higher in the THS 2.2 Menthol arm compared to mCC arm, and weighted average concentrations were 27% (95% CI: 1.3, 59.2; 11.20 ng/mL for THS 2.2 Menthol arm and 8.72 ng/mL for the mCC arm) higher in the THS 2.2 Menthol arm compared to mCC arm. For cotinine PK profile on Day 5, peak and weighted average plasma concentrations were 17% (95% CI: -5.1, 44.2; 192.10 ng/mL for the THS 2.2 Menthol arm and 163.42 ng/mL for the mCC arm) and 16% (95% CI: -6.3, 42.4; 171.25 ng/mL for the THS 2.2 Menthol arm and 147.39 ng/mL for the mCC arm) higher, respectively, for the THS 2.2 Menthol arm compared to the mCC arm. The median time to peak concentration on Day 5 was identical for the THS 2.2 Menthol and mCC arms for both nicotine (12 hours) and cotinine (16 hours).

Cytochrome P450 1A2 Activity

On Day 5, CYP1A2 activity had decreased from baseline by 22% and 24% in the THS 2.2 Menthol and SA arms, respectively; while in the mCC arm, CYP1A2 activity was 10% higher than baseline. During the Ambulatory Period, CYP1A2 activity remained decreased



with a 20% and 16% change from baseline in the THS 2.2 Menthol and SA arms, respectively, and increased from baseline in the mCC arm of 16% on Day 90.

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 28% (95% CI: 22.8, 32.9) lower than in subjects who continued to smoke mCC on Day 5, which was sustained during the Ambulatory Period with CYP1A2 activity 31% (95% CI: 22.3, 38.6) lower than mCC on Day 90. There was no notable difference in CYP1A2 activity between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102%; 95% CI: 95.4, 110.0 on Day 5; 92.48%; 95% CI: 82.0, 104.4 on Day 90).

Extent of Exposure – Product Use Consumption

At baseline (Day 0), the mean (95% CI) number of mCC consumed daily in the THS 2.2 Menthol and mCC arms (PP Set Period 1) was 13.1 (95% CI: 12, 14) and 12.5 (95% CI: 11, 14) mCC/day, respectively. During the Confinement Period, the number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm was lower than the number of mCC smoked at baseline with a mean of 11.4 (95% CI: 11, 12) sticks/day on Day 1 and then increased over the Confinement Period to 14.0 (95% CI: 13, 15) sticks/day on Day 5. Similarly, the daily consumption of mCC in the mCC arm decreased compared to baseline, with a mean of 11.0 (95% CI: 10, 12) mCC/day on Day 1, and then increased to 13.6 (95% CIs: 12, 15) mCC/day.

During the Ambulatory Period, in the THS 2.2 Menthol arm, the mean number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm returned to similar levels as baseline, with a mean 11.7 (95% CI: 10.2, 13.1), 12.7 (95% CI: 11.1, 14.2), and 12.7 (95% CI: 11.2, 14.3) sticks/day reported during PP Set Periods 2, 3, and 4, respectively. In the mCC arm, the mean number of mCC consumed daily during the Ambulatory Period remained higher as compared to baseline, with a mean 15.2 (95% CI: 13.5, 16.8) mCC/day reported during PP Set Period 4. For each product use period in the Ambulatory Period, the mean reported daily number of THS Menthol Tobacco Sticks was lower than the daily product use in mCC arm.

In the THS 2.2 Menthol arm, the use of mCC was negligible and the combined daily use of mCC and THS 2.2 Menthol over the Ambulatory Period was lower than the daily product use in the mCC arm.

The results for the PP Sets Periods 1, 2, 3, and 4 were similar to the Safety Population in each period.

Compliance to Product Use (FAS Population)

During the Confinement Period, as product use/regimen was fully controlled, 100% of subjects in each study arm (i.e., THS 2.2 Menthol, mCC, and SA) were compliant with their product regimen.



During the Ambulatory Period, in the THS 2.2 Menthol study arm at least 82.1% of subjects in each period exclusively used the assigned THS 2.2 Menthol product (100%). More than 85.9% of subjects in each period were classified as primarily THS 2.2 Menthol users (>95% of THS 2.2 Menthol arm). In the mCC arm all 41 subjects who completed the study, used the assigned product exclusively in each period, and in the SA study arm at least 92.5% remained abstinent in each period.

Risk markers (Clinical Risk Markers)

Risk Marker of Oxidative Stress: 8-epi-PGF_{2α} (Concentration Adjusted for Creatinine) (Day 90)

The levels of 8-epi-PGF_{2α} in subjects who switched to THS 2.2 Menthol were 12.7% (95% CI: 2.55, 21.81) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (92.8% ratio; 95% CI: 82.80, 103.96).

Risk Marker of Platelet Activation: 11-DTX-B2 (Concentration Adjusted for Creatinine) (Day 90)

The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 9.0% (95% CI: -2.94, 19.52) lower than that observed in subjects who continued to smoke mCC. The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 13% (95% CI: -0.53, 28.12) higher than that observed in subjects who abstained from smoking.

Risk Marker of Endothelial Dysfunction: sICAM-1 (Day 90)

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol use were 8.7% (95% CI: 2.05, 14.94) lower than that observed in subjects who continued to smoke mCC. There were no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102.4% ratio; 95% CI: 95.24, 110.12).

Risk Markers of Lipid Metabolism: LDL Cholesterol, HDL Cholesterol, Triglycerides, and Total Cholesterol (Day 90/Day of Discharge from Ambulatory Period)

The HDL cholesterol levels were increased by approximately 4.5 mg/dL (95% CI: 1.17, 7.88) in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-1.8 mg/dL difference; 95% CI: -5.28, 1.61).

For TGs, there were no notable differences observed between subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (-6.3 mg/dL difference; 95% CI: -21.20, 8.69). The levels in subjects who switched to THS 2.2 Menthol use was 18.7 mg/dL (95% CI: 2.99, 34.39) lower than in subjects who abstained from smoking.



There were no notable differences observed in the levels of TC or LDL cholesterol between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and compared to subjects who abstained from smoking.

Risk Markers of Inflammation: Platelets and White Blood Cell Differential Counts (Day of Discharge from Ambulatory Period)

There were no notable differences observed in platelet counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (102.9% ratio; 95% CI: 97.61, 108.57). The platelet counts were 6.2% (95% CI: 0.56, 12.28) higher in subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking.

Total WBC (leukocytes) counts in subjects who switched to THS 2.2 Menthol use were 0.6 GI/L (95% CI: 0.10, 1.04) lower than that observed in subjects who continued to smoke mCC. There were no notable differences observed in the leukocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.2 difference; 95% CI: -0.65, 0.33).

Neutrophils counts in subjects who switched to THS 2.2 Menthol use was 0.5 GI/L (95% CI: 0.08, 0.88) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.1 difference; 95% CI: -0.48 0.35).

Monocyte counts in subjects who switched to THS 2.2 Menthol use was 0.1 GI/L (95% CI: 0.01, 0.10) lower than that observed in subjects who continued to smoke mCC. There were no notable differences observed in the monocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking.

For lymphocytes, monocytes, eosinophils, and basophils there were no notable differences observed in counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC and compared to subjects who abstained from smoking.

Cardiovascular Risk: Homocysteine, hs-CRP, and Fibrinogen (Day 90)

For homocysteine and fibrinogen, there were no notable differences observed between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and subjects who abstained from smoking.

There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC for hs-CRP (93.6%; 95% CI: 62.23, 140.75). The levels of hs-CRP in subjects who switched to THS 2.2 Menthol use was 10.7% (95% CI: -27.33, 68.76) higher than that observed in subjects who abstained from smoking.

***Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure (Day of Discharge from Ambulatory Period)***

There were no notable differences observed in the systolic and diastolic blood pressure for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCCs, and compared to subjects who abstained from smoking.

Risk Markers of Metabolic Syndrome: Blood Glucose, Body Weight and Waist Circumference, and Hb1Ac (Day 90/Day of Discharge from Ambulatory Period)

For glucose, there were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (98.98% ratio; 95% CI: 96.42, 101.60). The levels of glucose in subjects who switched to THS 2.2 Menthol use was 2.80% (95% CI: 0.06, 5.61) higher than that observed in subjects who abstained from smoking.

For Hb1Ac, there were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC and compared to subjects who abstained from smoking.

For assessment of weight, there was no notable difference for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (-0.09 difference; 95% CI: -0.75, 0.57). The values in subjects who switched to THS 2.2 Menthol use were 1.24 kg (95% CI: 0.56, 1.92) lower than in subjects who abstained from smoking.

There were no notable differences observed in waist circumference between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC subjects who switched to THS 2.2 Menthol use and compared with subjects who abstained from smoking.

Risk Markers Associated with Respiratory Diseases

The value of FEV₁ (without bronchodilator) in subjects who switched to THS 2.2 Menthol use were 1.91 %pred (95% CI: -0.14, 3.97) higher than that observed in subjects who continued to smoke mCC. There were no notable differences observed in FEV₁ between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.02 difference; 95% CI: -2.15, 2.11).

Exploratory Endpoints**Ames Mutagenicity Test**

At baseline, mean Ames mutagenicity test values were comparable between the THS 2.2 Menthol and mCC arms (17293.80 and 15132.36 REV/24h, respectively) and lower in the



SA arm (14508.13 REV/24h). On Day 5, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values were approximately 2.3-fold and 1.6-fold lower than baseline, respectively; while in the mCC arm, Ames mutagenicity test values (REV/24h) were approximately 1.1-fold lower than baseline. Comparable reductions were observed on Day 90 in the THS 2.2 Menthol and SA arms, with mean values of approximately 2.6-fold and 1.8-fold lower than baseline, respectively; while in the mCC arm, Ames mutagenicity test values were approximately 1.1-fold higher than baseline.

Cytochrome P450 2A6 Activity

At baseline, CYP2A6 activity was comparable between study arms (range of 26.05% to 28.53%). There was no notable difference in CYP2A6 activity on the Day of Discharge (Confinement) between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (95% CI: 89.67, 107.96). On the Day of Discharge (Confinement), the CYP2A6 activity following THS 2.2 Menthol use was 64.33% (95% CI: 60.78, 67.56) lower than the activity observed in subjects who abstained from smoking.

There was no notable difference in the CYP2A6 activity on Day 90 between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (95% CI: 79.17, 123.12). On Day 90, the CYP2A6 activity following THS 2.2 Menthol use was 44.21% (95% CI: 29.98, 55.56) lower than the activity observed in subjects who abstained from smoking.

Fagerström Test for Nicotine Dependence on Day 90

For the THS 2.2 Menthol and the mCC arms, the majority of subjects had no apparent shift in FTND score, with 25 subjects (35.7%) for the THS 2.2 Menthol arm and 13 subjects (31.7%) for the mCC arm reporting a moderate dependence on nicotine at baseline and a moderate dependence on nicotine on Day 90. In the THS 2.2 Menthol arm, the next most frequent shift in FTND was mild to mild (18 subjects [25.7%]) and moderate to mild (9 subjects [12.9%]) between baseline and Day 90. In the SA arm, the highest proportion of subjects (29.7%) reported a moderate dependence at baseline and a mild dependence on Day 90.

Urge-to-smoke Symptoms (QSU-brief)

On Day 5, there were no notable differences in the QSU-brief urge-to-smoke total scores, Factor 1 scores, or Factor 2 scores between the subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. The urge-to-smoke overall and factor scores of subjects who switched to THS 2.2 Menthol use were lower than those subjects who abstained from smoking, with differences of -1.43 points (95% CI: -1.88, -0.98), -1.35 points (95% CI: -1.87, -0.84), and -1.50 points (95% CI: -1.95, -1.05) for QSU-brief total score, Factor 1 score, and Factor 2 score, respectively.



During the Ambulatory Period, considering the overall and individual time points, there were no notable differences between the QSU-brief urge-to-smoke total scores, Factor 1 scores, or Factor 2 scores for the subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, with 95% CIs for all parameters spanning 0.

The urge-to-smoke overall and factor scores of subjects who switched to THS 2.2 Menthol use were higher than that observed in subjects who abstained from smoking, with differences of 1.06 points (95% CI: 0.56, 1.55), 1.50 points (95% CI: 0.92, 2.07), and 0.63 points (95% CI: 0.16, 1.10) for QSU-brief total score, Factor 1 score, and Factor 2 score, respectively.

Minnesota Nicotine Withdrawal Scale

During the Confinement Period, the differences of THS 2.2 Menthol – mCC for MNWS-R total scores remained stable, with a difference of 0.11 (95% CI: -0.10, 0.31) on Day 5. Whereas, the differences of THS 2.2 Menthol – SA for MNWS-R total scores was -0.30 (95% CI: -0.51, -0.09) on Day 5.

During the Ambulatory Period, the differences of THS 2.2 Menthol – mCC for MNWS-R total scores remained stable, with a difference of 0.11 (95% CI: -0.09, 0.30) on Day 90. Whereas, the differences of THS 2.2 Menthol – SA for MNWS-R total scores were -0.18, -0.03, and 0.33 on Days 30, 60, and 90, respectively, with 95% CI on Day 90 of 0.12, 0.53.

Product Evaluation Questionnaire (MCEQ)

For craving, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, decreases from baseline were observed as early as Day 1 in the THS 2.2 Menthol arm, ranging from -3.4% (95% CI: -16.41, 9.60) to -23.8% (95% CI: -30.33, -17.18); whereas changes from baseline observed in the mCC arm ranged from 10.8% (95% CI: -1.11, 22.67) to -3.3% (95% CI: -10.44, 3.81). For the aversion subscale, a 16.3% (95% CI: 0.83, 31.69) increase from baseline was observed on Day 1 for the THS 2.2 Menthol study arm and 7.8% (95% CI: -10.35, 25.90) increase from baseline was observed on Day 1 for the mCC study arm.

Difference Between THS m2.2 and mCC Scores for MCEQ Subscales – PP Set		
MCEQ Subscale/ Time point	Difference THS m2.2 - mCC	
	Difference	95% CI
Aversion		
Day 1	0.07	-0.24, 0.37
Day 5	0.07	-0.23, 0.37
Day 90	-0.16	-0.49, 0.18
Craving reduction		
Day 1	-0.54	-1.05, -0.03



Day 5	-0.02	-0.55, 0.50
Day 90	-0.15	-0.62, 0.32
Enjoyment of respiratory tract sensation		
Day 1	-0.56	-0.96, -0.16
Day 5	-0.13	-0.55, 0.29
Day 90	0.30	-0.18, 0.78
Psychological reward		
Day 1	-0.41	-0.72, -0.10
Day 5	-0.21	-0.51, 0.10
Day 90	0.00	-0.37, 0.36
Smoking satisfaction		
Day 1	-0.86	-1.26, -0.47
Day 5	-0.39	-0.81, 0.03
Day 90	0.01	-0.39, 0.41
Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.		

On Day 1, the mean scores for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales were lower in subjects who switched to THS 2.2 Menthol use compared to those observed in subjects who continued to smoke mCC (THS m2.2 – mCC difference: -0.5 for craving reduction; -0.6 for enjoyment respiratory tract sensation; -0.4 for psychological reward; -0.9 for smoking satisfaction). By the end of the Exposure Period the THS 2.2 Menthol and mCC arm differences became less for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, with differences on Day 5 of -0.02, -0.13, -0.21, and -0.39, respectively, and differences on Day 90 of -0.15, 0.30, 0.00, and 0.01, respectively.

On Days 5 and 90, there were no notable differences between subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC for aversion subscale.

Human Smoking Topography (Day 90)

The total puff volume was similar between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (-23.5 mL difference; 95% CI: -141.54, 94.61). The total smoking duration was approximately 3.4 minutes for both arms (1.84 s difference; 95% CI: -35.93, 32.24) while an increase in puff frequency of 1.03 puffs/min (95% CI: 0.11, 1.94) was observed in subjects using THS 2.2 Menthol use in comparison with subjects who continued to smoke mCC.

An 8.46 mL/s (95% CI: 4.98, 11.94) lower average flow was found in THS 2.2 Menthol, with a 0.26 s (95% CI: -0.02, 0.54) longer average puff duration.



This was the result of an adaptation process for subjects using THS 2.2 Menthol who, compared to subjects in the mCC arm, increased the total number of puffs (3.19 puffs difference; 95% CI: 0.49, 5.89) and compensated with a 9.67 mL (95% CI: 3.48, 15.87) lower average puff volume.

Visual Inspection of the THS Tobacco Plugs and Filter Analysis

On all study days during the Confinement Period, more than 93.3% of THS Tobacco Plugs assessed by visual inspection showed no overheating (grade 0), with a proportion ranging from 0.6% to 1.4% only exhibiting white spot(s) inside the tobacco plug (grade 1). Among more than 4000 of the THS Tobacco Plugs analyzed, there was only 1 occurrence of ashes inside the THS Tobacco plug and burnt paper (grade 2). During the Ambulatory Period, the majority of THS Tobacco Plugs ($\geq 98.2\%$ each day) showed grade 0. The proportion of grade 1 was similar across all study days (range 0.6% to 1.1%). There were no occurrences of a grade 2.

Summary

All BoExp (except S-BMA and NEQ) showed a mean level in the THS 2.2 Menthol study arm substantially lower than for the mCC arm on Day 5 (full range was 49% to 94% lower) and Day 90 (full range was 41% to 94% lower). The magnitude of reduction observed was similar to that observed in the SA arm for these BoExp, except for 3-HPMA, Total NNAL, and Total NNN. In addition, the decrease in urine mutagenicity related to THS 2.2 Menthol use provided additional information on reduced exposure.

THS 2.2 Menthol use for 3 months resulted in favorable changes, which followed the trajectory of SA arm, for some CREs which were selected as indicators of mechanistic pathways affected by smoking (i.e., HDL cholesterol: lipid pathway; 8-epi-PGF_{2α}: oxidative stress; 11-DTX-B2: platelet activation; sICAM-1: endothelial dysfunction; WBC: inflammation). The CREs intended to monitor cardiovascular risk did not show any difference suggesting no change in cardiovascular risk during the study. These data indicate that exposure reduction achieved with switching to THS 2.2 Menthol may translate into reduced risk of smoking-related diseases with prolonged use of THS 2.2 Menthol over time.



The evaluation of subjective effects during the study demonstrated that there were no notable differences between the subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC during the study for the total scores in the QSU-brief urge-to-smoke questionnaire; however, on Day 5, the urge-to-smoke scores of subjects who switched to THS 2.2 Menthol use were lower than in subjects who abstained from smoking, but were higher on Day 90. For the MNWS-R total scores on Day 1, subjects who switched to THS 2.2 Menthol use generally had lower scores compared to subjects who abstained from smoking, with the differences between the THS 2.2 Menthol and SA arms reducing over time during the study. For the MCEQ subscales on Day 1, subjects who switched to THS 2.2 Menthol use generally had lower scores compared to subjects who continued to smoke mCC, with the differences between THS 2.2 Menthol and mCC arms reducing over time during the study for subscales such as psychological reward and smoking satisfaction; and on Day 90, enjoyment of respiratory tract sensation in subjects who switched to THS 2.2 Menthol use was higher than that observed in subjects who continued to smoke mCC.

For HST parameters, total product use duration was similar between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, at approximately 3.4 minutes (1.84 s difference; 95% CI: -35.93, 32.24). In addition, total puff volume was similar between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC. The average puff volume was 9.67 mL (95% CI: -15.87, -3.48) lower in subjects who switched to THS 2.2 Menthol use compared to that observed in subjects who continued to smoke mCC, due to a lower average flow.

Adaptation to THS 2.2 Menthol was observed from Day 1, with subjects who switched to THS 2.2 Menthol having higher average puff duration, lower average flow, and lower average puff volume. Results observed on Day 1 remained stable until Day 90.



12 SAFETY EVALUATIONS

The safety endpoints were analyzed using the safety populations. The overall Safety Population contained 175 subjects: 160 randomized subjects and 15 subjects who were exposed to THS 2.2 Menthol from the product test but were not randomized; the data pertaining to that latter population subset are included on the pre-randomization tables. The post-randomization Safety Population consisted of 160 randomized subjects (78 subjects in the THS 2.2 Menthol arm, 42 subjects in the mCC arm, and 40 subjects in the SA arm).

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 tabulated for the Safety Population for pre- and post-randomization and for the Confinement and Ambulatory Periods in [Appendix 15, Table 15.2.6.1.1](#). A summary of AEs during the pre-randomization period is also presented in [Table 130](#). A summary of AEs reported post-randomization (Confinement and Ambulatory Periods) by study arm are also presented in [Table 131](#). A summary of AEs for the Safety Population by product use category in the Ambulatory Period is tabulated in [Appendix 15, Table 15.2.6.2.1](#) and is also presented in [Table 132](#).

**Table 130 Summary of Adverse Events (Safety Population) – Pre-randomization**

	Study Arm			Product Test only (N=15)	Overall Safety (N=175)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)		
Number of:					
AEs	6	4	3	9	22
SAEs	0	0	0	0	0
Severe AEs	0	0	0	0	0
AEs leading to discontinuation	0	0	0	2	2
AEs related to IP	0	0	0	0	0
AEs related to study procedures	1	0	1	0	2
Number (%) of subjects with:					
AEs	6 (7.7%)	3 (7.1%)	3 (7.5%)	4 (26.7%)	16 (9.1%)
AEs related to IP	0	0	0	0	0
AEs related to study procedures	1 (1.3%)	0	1 (2.5%)	0	2 (1.1%)

Abbreviations: AE = adverse event; IP = investigational product (THS m2.2 or mCC); mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; SAE = serious adverse event; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.1.1](#)

**Table 131 Summary of Adverse Events (Safety Population) – Post-randomization**

	Study Arm			Overall (N=160)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)	
Number of:				
AEs	49	22	22	93
SAEs	0	0	0	0
Severe AEs	0	0	0	0
AEs leading to discontinuation	0	0	0	0
AEs related to IP	1	0	0	1
AEs related to study procedures	1	2	3	6
Number (%) of subjects with:				
AEs	32 (41.0%)	14 (33.3%)	14 (35.0%)	60 (37.5%)
AEs related to IP	1 (1.3%)	0	0	1 (0.6%)
AEs related to study procedures	1 (1.3%)	2 (4.8%)	3 (7.5%)	6 (3.8%)

Abbreviations: AE = adverse event; IP = investigational product (THS m2.2 or mCC); mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; SAE = serious adverse event; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.1.1.](#)

**Table 132 Summary of Adverse Events (Safety Population) by Product Use Category – Ambulatory Period**

	Study Arm				
	THS m2.2 (N=78)		mCC (N=42)	SA (N=40)	
	THS m2.2 (N=71)	Not abstinent (N=5)	mCC (N=41)	Abstinent (N=38)	Predominantly abstinent (N=1)
Number of:					
AEs	32	8	20	12	0
SAEs	0	0	0	0	0
Severe AEs	0	0	0	0	-
AEs leading to discontinuation	0	0	0	0	-
AEs related to IP	0	0	0	0	-
AEs related to study procedures	1	0	1	0	-
Number (%) of subjects with:					
AEs	26 (36.6%)	3 (60.0%)	14 (34.1%)	9 (23.7%)	-
AEs related to IP	0	0	0	0	-
AEs related to study procedures	1 (1.4%)	0	1 (2.4%)	0	-

Abbreviations: AE = adverse event; IP = investigational product (THS m2.2 or mCC); mCC = menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; SAE = serious adverse event; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.2.1](#)

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

Two subjects who were enrolled and exposed to the THS 2.2 Menthol product during the product test were discontinued due to AEs and therefore were not randomized ([Table 130](#)). The 2 subjects experienced AEs of nasopharyngitis and hypotension ([Appendix 15, Table 15.2.6.7.1](#)).

Overall, the majority of the AEs were mild in severity, with 93 AEs reported post-randomization in 60 of the 160 subjects (37.5%) in the Safety Population. Prior to randomization there were 22 AEs reported in 16 of 175 subjects (9.1%), with the majority of AEs reported as mild.

The majority of AEs were mild; 91 of 93 AEs reported were mild and 2 AEs were moderate.



The incidence of AEs was low, with 49 AEs reported by 32 subjects (41.0%) in the THS 2.2 Menthol arm, 22 AEs reported by 14 subjects (33.3%) in the mCC arm, and 22 AEs reported by 14 subjects (35.0%) in the SA arm. In addition, of those AEs reported during the Ambulatory Period in the THS 2.2 Menthol arm, the majority were reported by subjects considered to be primarily THS 2.2 Menthol users. All subjects who reported AEs in the mCC and SA arms were mCC users and abstinent, respectively ([Table 132](#)).

During the study, only 1 AE reported by 1 (1.3%) subject in the THS 2.2 Menthol arm was considered related to the IP; this AE of diarrhea was not expected.

Eight AEs were reported during the study as considered to be related to study procedures; 1 AE was reported as considered to be related to the IP. In addition, 2 pre-randomization AEs reported by 2 subjects (1.1%) were considered related to study procedures and no pre-randomization AEs were considered related to the IP ([Table 130](#)).

For subjects enrolled at the Seishukai Clinic, for which AEs have been only listed, there were a total of 14 AEs in 12 subjects following product exposure. None were related to the IP, and were all mild in severity.

12.1.2 Display of Adverse Events

Adverse events are tabulated by study arm for the Safety Population by SOC and PT in [Appendix 15, Table 15.2.6.3.1](#). A summary of AEs reported post-randomization by SOC and PT are also provided in [Table 133](#). A summary of AEs for the Safety Population by product use category, SOC, and PT is tabulated in [Appendix 15, Table 15.2.6.4.1](#).

**Table 133 Summary of Adverse Events by System Organ Class and Preferred Term Reported by ≥ 2 Subjects (Safety Population) – Post-randomization**

System Organ Class Preferred Term	Study Arm			Overall (N=160)
	THS m2.2 (N=78)	mCC (N=42)	SA (N=40)	
Number (%) of subjects with any AEs	32 (41.0%)	14 (33.3%)	14 (35.0%)	60 (37.5%)
Investigations	24 (30.8%)	8 (19.0%)	10 (25.0%)	42 (26.3%)
Haemoglobin decreased	11 (14.1%)	3 (7.1%)	3 (7.5%)	17 (10.6%)
Neutrophil count decreased	5 (6.4%)	1 (2.4%)	2 (5.0%)	8 (5.0%)
Blood triglycerides increased	3 (3.8%)	1 (2.4%)	2 (5.0%)	6 (3.8%)
White blood cell count decreased	2 (2.6%)	0	1 (2.5%)	3 (1.9%)
Alanine aminotransferase increased	1 (1.3%)	0	1 (2.5%)	2 (1.3%)
Gamma-glutamyltransferase increased	2 (2.6%)	0	0	2 (1.3%)
Protein urine present	0	1 (2.4%)	1 (2.5%)	2 (1.3%)
Infections and infestations	6 (7.7%)	3 (7.1%)	3 (7.5%)	12 (7.5%)
Nasopharyngitis	3 (3.8%)	1 (2.4%)	2 (5.0%)	6 (3.8%)
Hordeolum	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Pharyngitis	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Gastrointestinal disorders	4 (5.1%)	2 (4.8%)	1 (2.5%)	7 (4.4%)
Constipation	2 (2.6%)	1 (2.4%)	1 (2.5%)	4 (2.5%)
Ear and labyrinth disorders	0	0	2 (5.0%)	2 (1.3%)
Vertigo	0	0	2 (5.0%)	2 (1.3%)
Psychiatric disorders	0	1 (2.4%)	1 (2.5%)	2 (1.3%)
Insomnia	0	1 (2.4%)	1 (2.5%)	2 (1.3%)

Abbreviations: AE = adverse event; mCC = menthol conventional cigarette; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; PT = preferred term; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Terms coded using MedDRA® Version 16.0.

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

Data Source: [Appendix 15, Table 15.2.6.3.1.](#)

During the pre-randomization period, the most frequently reported AEs by SOC of the 22 AEs reported, was Investigations, followed by Infections and Infestations. With the majority of AEs reported by 1 subject only, decreased neutrophil count, increased blood TGs, and headache were the most frequently reported (5, 2, and 2 subjects, respectively).

Overall, the most frequent AEs by SOC in all study arms post-randomization were Investigations, which were experienced by 3/78 subjects (3.8%) in the THS 2.2 Menthol



arm, 1/42 subjects (2.4%) in the mCC arm, and 2/40 subjects (5.0%) in the SA arm during the Confinement Period, and by 23/78 subjects (29.5%) in the THS 2.2 Menthol arm, 8/42 subjects (19.0%) in the mCC arm, and 8/40 subjects (20.0%) in the SA arm during the Ambulatory Period. During the study, all other AEs by SOC were experienced by $\leq 5.6\%$ subjects in each study arm.

The most frequent AE by PT reported in the Ambulatory Period was decreased hemoglobin, which was reported in 11/78 subjects (14.1%) in the THS 2.2 Menthol arm, 3/42 subjects (7.1%) in the mCC arm, and 3/40 subjects (7.5%) in the SA arm. Decreased neutrophils and increased blood TGs were also reported by $\geq 5.0\%$ of subjects in a study arm: decreased neutrophils were reported in 4/78 subjects (5.1%) in the THS 2.2 Menthol arm, 1/42 subjects (2.4%) in the mCC arm, and 2/40 subjects (5.0%) in the SA arm; and increased blood TGs were reported in 3/78 subjects (3.8%) in the THS 2.2 Menthol arm, 1/42 subjects (2.4%) in the mCC arm, and 2/40 subjects (5.0%) in the SA arm.

12.1.3 Analysis of Adverse Events

12.1.3.1 Analysis of Adverse Events of Severity

Adverse events are summarized by severity (mild, moderate, or severe), SOC, and PT for the Safety Population by study arm in [Appendix 15, Table 15.2.6.10.1](#), and by severity, product use category, SOC, and PT for the Safety Population by study arm in [Appendix 15, Table 15.2.6.11.1](#).

The majority of AEs were mild; 20 of 21 AEs reported during the Confinement Period were mild and 1 AE of periodontitis, reported in the SA arm, was considered moderate. Seventy-one of the 72 AEs reported during the Ambulatory Period were mild and 1 AE of uterine leiomyoma, reported in the mCC arm, was considered moderate.

12.1.3.2 Analysis of Adverse Events by Relationship

12.1.3.2.1 Adverse Events Related to Investigational Product

Adverse events related to IP (THS 2.2 Menthol or mCC) and expectedness are summarized by SOC and PT for the Safety Population in [Appendix 15, Table 15.2.6.5.1](#), and by product use category, SOC, and PT in [Appendix 15, Table 15.2.6.6.1](#).

Overall, only 1 AE was considered related to IP during the study; 1 subject in the THS 2.2 Menthol arm experienced diarrhea in the Confinement Period, which was considered related to IP and was not expected.

No AEs (post-randomization) led to study product discontinuation, interruption, or reduction ([Appendix 15, Table 15.2.6.7.1](#) and [Table 15.2.6.8.1](#)).



12.1.3.2.2 Adverse Events Related to Study Procedure

Adverse events related to study procedures are summarized by SOC and PT for the Safety Population in [Appendix 15, Table 15.2.6.9.1](#).

Two pre-randomization AEs of hunger (in the SA arm) and dysphoria (in the THS 2.2 Menthol arm) were considered related to study procedures. During the Confinement Period, AEs considered related to study procedures were: 2 AEs of constipation (1 reported in each of the mCC and SA arms), 1 AE of insomnia (reported in the SA arm), and 1 AE of vertigo (reported in the SA arm). During the Ambulatory Period, AEs considered related to study procedures were: 1 AE of constipation in the THS 2.2 Menthol arm and 1 AE of insomnia in the mCC arm.

No AEs related to study procedures led to subject discontinuation.

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 study arm for the Safety Population in [Appendix 15, Table 15.2.6.15.1](#) and in [Table 134](#).

**Table 134 Summary of THS 2.2 Menthol Device Events and Malfunctions (THS 2.2 Menthol Study Arm) – Post-randomization**

	THS m2.2 (N=78)	
	n (%)	Events
Number (%) subjects with any device events and malfunctions	53 (67.9%)	144
Is not related to adverse event	53 (67.9%)	144
Major	53 (67.9%)	144
Charger heater broken (Light emitting device [LED] blinking red)	32 (41.0%)	50
Charger does not charge when inserted into the mobile unit	23 (29.5%)	40
Battery malfunction	17 (21.8%)	26
Charger stops heating before end of smoking experience	5 (6.4%)	5
Smoking experience does not start when pressing the button	4 (5.1%)	4
The device has charging failure due to bad electrical contact between Charger and Holder	4 (5.1%)	4
The subject lost it	3 (3.8%)	4
Electronic malfunction during the smoking experience	2 (2.6%)	3
The cover of LED display was fallen off	1 (1.3%)	1
Subject informed that she lost the Holder via telephone on 25/sep.new Holder was shipped on 25/sep.we confirmed she received new Holder and instructed her not to lose it via teleph	1 (1.3%)	1
The cover of charger doesn't close	1 (1.3%)	1
The patient dropped the device into water and destroyed it	1 (1.3%)	1
The patient lost the device	1 (1.3%)	2
The subject lost this device	1 (1.3%)	2

Abbreviations: N = number of subjects; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

Data Source: [Appendix 15, Table 15.2.6.15.1](#).

During THS 2.2 Menthol use in the Confinement Period, 26 subjects reported a total of 39 major device events or malfunctions. During THS 2.2 Menthol use in the Ambulatory Period, 44 subjects reported a total of 105 major device events or malfunctions. None of these events led to an AE. The most frequently reported type of device events or malfunctions during the Confinement and Ambulatory Periods were the same: charger heater broken, charger does not charge when inserted into the mobile unit, and battery 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 discontinuation from the study are listed in [Appendix 15, Listing 15.3.6.1.2](#) and [Listing 15.3.6.1.3](#), respectively.

12.2.1.1 Deaths

No deaths occurred in this study.

12.2.1.2 Other Serious Adverse Events

No SAEs occurred during this study for any subject.

12.2.1.3 Other Significant Adverse Events

Adverse events leading to product discontinuation, interruption, or reduction are summarized by SOC and PT for the Safety Population by study arm in [Appendix 15, Table 15.2.6.7.1](#).

There were no AEs leading to study discontinuation in any randomized subject.

Two subjects who were exposed at the THS 2.2 Menthol product test, but not randomized were discontinued due to AEs of nasopharyngitis and hypotension. Both AEs were mild and not considered related to the IP or study procedures.

12.2.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths, SAEs, or other significant post-randomization 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 post-randomization 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 baseline (Day 0) to Day of Discharge from the Ambulatory Period, and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Clinical chemistry data are summarized for the Safety Population in [Appendix 15, Table 15.2.6.16.1](#) including summaries of low, normal, high, and abnormal clinically relevant results.

A total of 33 results from 16 subjects (10.0%), which were deemed to be clinically relevant by the Principal Investigator, were reported for the clinical chemistry values during the study. Of these, 31 results from 15 subjects were reported after the product test at Admission. The majority of subjects in all study arms had normal clinical chemistry values at each time point (the lowest percentage of normal values was 70.3%, which was observed for cholesterol at Screening). In general, mean changes from baseline in clinical chemistry parameters were small and comparable between study arms.

Shifts in clinical chemistry parameters, in which ≥ 2 subjects in any study arm had a shift from normal to low, included sICAM-1, homocysteine, protein, glucose, TC, LDL cholesterol, fibrinogen, gamma-glutamyl aminotransferase (GGT), bilirubin, and alanine aminotransferase (ALT). Normal to low shifts were seen across all study arms for sICAM-1, protein, glucose, TC, LDL cholesterol, and GGT; in the THS 2.2 Menthol and mCC arms only for homocysteine and fibrinogen; in the mCC and SA arms only for bilirubin; and in the SA arm only for ALT.

Shifts from baseline, in which ≥ 2 subjects in any study arm had a shift from normal to high, included TC, LDL cholesterol, HDL cholesterol, homocysteine, aspartate aminotransferase (AST), ALT, GGT, TGs, fibrinogen, sICAM-1, glucose, hs-CRP, bilirubin, and albumin. Normal to high shifts were seen across all study arms for TC, LDL cholesterol, homocysteine, AST, ALT, GGT, TGs, fibrinogen, sICAM-1, glucose, and hs-CRP; in the THS 2.2 Menthol and SA arms only for HDL cholesterol and bilirubin; and in the mCC and SA arms only for albumin.

The majority of clinical chemistry variables were normal or classified as grade 1 (mild) on the toxicity grading. The following subjects reported clinical chemistry variables classified as grade 2 (moderate) on the toxicity grading, after the time of product test at Admission.

In the THS 2.2 Menthol arm:

- Subject TOK-0001: TC of 311 mg/dL (grade 2) on Day 60 and 311 mg/dL (grade 2) on Day 91/Discharge Ambulatory.



- Subject TOK-0083: ALT of 111 IU/L (grade 2) on Day 30, and GGT of 130 IU/L on Day 30.
- Subject TOK-0179: TGs of 380 mg/dL (grade 2) on Day 6/Discharge Confinement, and 343 mg/dL (grade 2) on Day 91/Discharge Ambulatory.
- Subject TOK-0241: TGs of 304 mg/dL (grade 2) at Screening, 421 mg/dL (grade 2) on Day 0, 343 mg/dL (grade 2) on Day 6/Discharge Confinement, 396 mg/dL (grade 2) on Day 30, and 359 mg/dL (grade 2) on Day 60.
- Subject TOK-0248: TGs of 408 mg/dL (grade 2) on Day 0 and 491 mg/dL (grade 2) on Day 91/Discharge Ambulatory.
- Subject TOK-0266: TGs of 368 mg/dL (grade 2) on Day 60 and 344 mg/dL (grade 2) on Day 91/Discharge Ambulatory.
- Subject TOK-0449: TGs of 367 mg/dL (grade 2) on Day 0, 368 mg/dL (grade 2) on Day 6/Discharge Confinement, 421 mg/dL (grade 2) on Day 30, 347 mg/dL (grade 2) on Day 60, 421 mg/dL (grade 2) on Day 91/Discharge Ambulatory, and 2 further unscheduled grade 2 values of 486 mg/dL and 324 mg/dL following Day 91/Discharge Ambulatory.

In the mCC arm:

- Subject TOK-0012: protein of 5.4 g/dL (grade 2) on Day 30.
- Subject TOK-0026: TC of 343 mg/dL (grade 2) on Day 0.
- Subject TOK-0350: TGs of 359 mg/dL (grade 2) on Day 60.

In the SA arm:

- Subject TOK-0452: TGs of 353 mg/dL (grade 2) on Day 91/Discharge Ambulatory and an unscheduled grade 2 value of 304 mg/dL following Day 91/Discharge Ambulatory.

For Subjects TOK-0179, TOK-0248, TOK-0266, TOK-0273, TOK-0449, TOK-0350, and TOK-0452, increased TGs were reported as AEs (blood TGs increased). For Subjects TOK-0001 and TOK-0026, increased cholesterol was reported as an AE (blood TC increased). For Subject TOK-0083, increased ALT and increased GGT were reported as AEs (ALT increased and GGT increased, respectively). For Subject TOK-0012, decreased protein was reported as an AE (protein total decreased). For Subject TOK-0278, increased ALT was reported as AEs (ALT increased). Each event was mild in severity and not considered to be related to the IP or study procedures, and the majority of cases were reported in the Ambulatory Period.

No subjects reported clinical chemistry values classified as grade 3 (severe).



12.3.2 Hematology

Hematology data are presented by subject in [Appendix 15, Listing 15.3.6.5](#) including individual changes and shifts from baseline (Day 0) to Day of Discharge from the Ambulatory Period, and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Hematology data are summarized for the Safety Population in [Appendix 15, Table 15.2.6.17.1](#) including summaries of low, normal, high, and abnormal clinically relevant results.

A total of 70 results from 26 subjects (16.25%) which were deemed to be clinically relevant by the Principal Investigator were reported for the hematology values during the study. Thirty-seven were reported in the THS 2.2 Menthol arm, 22 in the mCC arm, and 11 in the SA arm. All of these results were reported after the product test at Admission. The majority of subjects in all study arms had normal hematology values at each time point (the lowest percentage of normal values was 73.1%, which was observed for erythrocytes on Day 30). In general, mean changes from baseline in hematology parameters were small and comparable between study arms.

Shifts in hematology parameters in which ≥ 2 subjects in any study arm had a shift from normal to low included erythrocytes, hemoglobin, erythrocyte mean corpuscular hemoglobin concentration, neutrophils, hematocrit, leukocytes (total WBC count), and monocytes. Normal to low shifts for all of these parameters were seen across all study arms.

Shifts from baseline in which ≥ 2 subjects in any study arm had a shift from normal to high included neutrophils, and erythrocyte mean corpuscular volume. Normal to high shifts for all of these parameters were seen across all study arms.

The majority of hematology variables were normal or classified as grade 1 (mild) on the toxicity grading. However, there were 67 values classified as grade 2 (moderate) on the toxicity grading, and 13 values classified as grade 3 (severe) on the toxicity grading.

Those classified as grade 2 included hemoglobin decreased, WBC decreased, lymphocytes increased and decreased, eosinophils increased, and neutrophil decreased. Those that were classified as grade 3 were all hemoglobin values, with 8 values reported for the THS 2.2 Menthol arm (2, 3, and 3 on Days 30, 60, and 91, respectively), 4 values reported for the mCC arm (1, 2, and 1 on Days 30, 60, and 91, respectively), and 1 value reported for the SA arm (0, 0, and 1 on Days 30, 60, and 91, respectively).

As described in [Section 12.1.2](#), for the THS 2.2 Menthol arm there were 2 AEs for hematology parameters reported during the Confinement Period (1 AE of neutrophil decreased and 1 AE of WBC count decreased) and 19 AEs during the Ambulatory Period (13 AEs of hemoglobin decreased, 4 AEs of neutrophils decreased, 1 AE of WBC count



decreased, and 1 AE of lymphocyte count decreased). In the mCC arm, there was 1 AE of hemoglobin decreased reported during the Confinement Period and 4 AEs of hematology parameters reported during the Ambulatory Period (1 AE of lymphocyte count increased, 1 AE of neutrophil decreased, and 3 AEs of hemoglobin decreased). In the SA arm, there was 1 AE of WBC count decreased during the Confinement Period and 6 AEs for hematology parameters reported during the Ambulatory Period (3 AEs of hemoglobin decreased, 2 AEs of neutrophil decreased, and 1 AE of eosinophil increased).

All post-randomization AEs for hematology parameters were considered mild in severity and all were considered not related to the IP and study procedures.

12.3.3 Urinalysis

Urinalysis data are presented by subject in [Appendix 15, Listing 15.3.6.6](#) including individual changes and shifts from baseline (Day 0 or Screening) to Discharge in the Ambulatory Period and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Urinalysis data are summarized for the Safety Population in [Appendix 15, Table 15.2.6.18.1](#) including summaries of low, normal, high, and abnormal clinically significant results.

The majority of subjects in all study arms had normal urinalysis values during the study (the lowest percentage of normal values was 44.4%, which was observed for protein urine [negative] at the end of the Confinement Period [Day 6]). In general, urinalysis results were comparable between study arms and any mean changes from baseline in pH and specific gravity were small and comparable between study arms.

For protein present in urine parameter, there were a number of values classified as grade 1 and 2 classified as grade 2. The greatest number of grade 1 values for this parameter were present on Day 6/Discharge Confinement (21 values), with 12, 5, and 4 grade 1 values in the THS 2.2 Menthol arm, mCC arm, and SA arm, respectively. The majority of the values were not clinically significant.

There were 3 clinically relevant abnormalities observed, which were classified as grade 2 on the toxicity scale; 2 values for protein urine and 1 value for glucose urine. These corresponded to 2 AEs reported during the study:

- Subject TOK-0036 of the THS 2.2 Menthol arm had an AE of glucose present in urine reported on Day 90 (grade 2), which was ongoing at the end of the study. It was considered to be mild in severity and not related to the IP or study procedures. It coincided with an AE of blood glucose increased, which was reported on the same day.



- Subject TOK-0350 of the mCC arm had an AE of protein present in urine reported on Day 61 (grade 2), and it was considered resolved by Day 91/Discharge Ambulatory (31 days). It was considered to be mild in severity and not related to the IP or study procedures.
- Subject TOK-0148 of the SA arm had an AE of protein present in urine reported on Day 91/Discharge Ambulatory (grade 2), which was ongoing at the end of the study. It was considered to be mild in severity and not related to the IP or study procedures.

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 and shifts from baseline.

Vital signs data are summarized for the Safety Populations in [Appendix 15, Table 15.2.6.20](#) including summaries of changes from baseline at each assessment time point.

The mean and median for all vital signs analyzed were unremarkable and comparable between study arms ([Section 11.2.6.7](#)). In general, mean changes from baseline in vital signs parameters were small and comparable between study arms, with the exception of pulse rate during the Confinement Period for the SA arm. Mean and median changes from baseline in pulse rate for the SA arm, from Day 1 to Day 6/Discharge Confinement, were marginally greater than those observed at the same time points for the THS 2.2 Menthol and mCC arms. In the SA arm the maximum mean (SD) change from baseline was -12.3 (7.61) beats/min on Day 6/Discharge Confinement compared to -5.5 (8.31) and -4.3 (6.66) beats/min for the THS 2.2 Menthol and mCC arms, respectively. During the Ambulatory Period, these differences between the study arms were no longer observed.

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](#).

Weight and BMI data are summarized for the Safety Population in [Appendix 15, Table 15.2.6.24](#).



In all study arms, there were in the majority of cases no clinically relevant physical examination findings recorded during the Confinement or Ambulatory Periods; however, there were 6 occurrences in 5 subjects where abnormal findings were considered to be clinically significant:

- On Day 6/Discharge Confinement, Subject TOK-0044 of the THS 2.2 Menthol arm was found to have rectal prolapse caused by constipation. Constipation and rectal prolapse were both reported as AEs, considered mild in severity, and were resolved within 1 day. Neither were considered to be related to the IP or study procedure.
- On Day 60, Subject TOK-0099 of the THS 2.2 Menthol arm had a stuffy nose and temperature of 37.7°C reported at the physical examination and was consistent with the AE of common cold, which was reported on Day 59. The AE resolved within 2 days, was considered to be mild in severity, and was not considered related to the IP or study procedure.
- On Days 60 and 91, Subject TOK-0449 of the THS 2.2 Menthol arm had a tooth fracture, which was reported as an AE from Day 60. This physical finding was still present at an unscheduled follow-up visit on Day 105, and was reported as resolved 1 day later. The AE was considered to be mild in severity and not related to the IP and study procedure.
- On Day 6/Discharge Confinement, Subject TOK-0246 of the SA arm had parotitis, which was reported as an AE on Day 0. It was resolved by Day 13, was considered moderate in severity, and was not considered to be related to the IP or study procedure.
- On Day 60, Subject TOK-0273 of the SA arm had a fracture of the left middle finger, which was reported as an AE on Day 45. It was considered to be resolved by Day 91/Discharge Ambulatory. The AE was considered mild in severity and not related to the IP or study procedure.

There were also 3 subjects that were exposed to the test product but were not randomized that had physical exam findings that were considered clinically significant.

Mean body weight and BMI were comparable between study arms and changes from baseline were small and comparable between study arms.

12.4.3 Electrocardiogram

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 15.2.6.21](#) 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 study arms.

No subject reported an abnormal ECG finding, or finding that had shifted from normal to abnormal compared with baseline that was considered to be clinically significant.

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 15.2.6.22](#) including summaries of changes from baseline to Day of Discharge.

In all study arms, the majority of baseline spirometry assessments were normal, with 2, 1, and 3 assessments for the THS 2.2 Menthol, mCC, and SA arms classified as abnormal but not clinically significant. When spirometry was assessed again at the end of the Confinement Period (Day of Discharge from the Confinement Period) and at the end of the Ambulatory Period (Day of Discharge from the Ambulatory Period) the majority of assessments were normal, and the number of abnormal assessments had marginally decreased from that observed at baseline (overall, 6 abnormal assessments were observed at baseline, and 2 on the Day of Discharge from the Ambulatory Period). For all study arms, no clinically significant spirometry results were observed on Day 5 or Day 90 Visit assessments.

In all study arms, all subjects had post-bronchodilator $FEV_1/FVC \geq 0.70$, post-bronchodilator $FEV_1 \geq 80.1\%$ of predicted, and post-bronchodilator $FVC \geq 80.2\%$ of predicted at Screening.

12.4.5 Cough

Subject listings for the assessment of cough are presented by subject in [Appendix 15, Listing 15.3.6.15](#).

The results for the assessment of cough intensity, frequency, and amount of sputum production during the study using the Likert scales are summarized for the Safety Population in [Appendix 15, Table 15.2.6.25](#). 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 15.2.6.25.1](#).



Overall, the number of randomized subjects who experienced a cough during the study was high (98 subjects, 61.3%). Cough was also experienced by the enrolled but not randomized subjects (5 subjects, 33.3%). The incidence of cough between the THS 2.2 Menthol, mCC, and SA arms was 67.9%, 57.1%, and 52.5%, respectively.

Cough intensity and frequency of cough were comparable between THS 2.2 Menthol and mCC arms, with the most commonly reported cough intensity overall being very mild (47.2% and 54.2%, respectively) and the most common frequency being rarely (49.1% and 54.2%, respectively). In the SA arm the most commonly reported cough intensity overall was mild (42.9%) and the most commonly reported frequency overall was sometimes (42.9%). The highest intensity of cough experienced during the study was moderate, which was reported at a similar incidence in all the study arms (17.0%, 12.5%, and 19.0%, for THS 2.2 Menthol, mCC, and SA arms respectively). The highest frequency of cough experienced during the study was often, which was reported by 1 subject in the THS 2.2 Menthol arm (1 event in 1 subject [1.9%]).

All subjects who experienced cough reported either no sputum or a moderate amount of sputum. The most frequently reported amount of sputum in the THS 2.2 Menthol and mCC arms was no sputum (56.6% and 58.3%, respectively). The subjects in the SA arm who experienced a cough most frequently reported a moderate amount of sputum (52.4%). All enrolled but not randomized subjects who experienced a cough reported no sputum.

The mean percentage of subjects experiencing a cough during the study decreased over time in the 3 study arms, with a greater decrease observed in the THS 2.2 Menthol and SA arms compared to the mCC arm: at Days 0, 5, and 90, 50%, 42.3%, and 19.2% of subjects in the THS 2.2 Menthol study arm, respectively; 42.9%, 35.7%, and 31.0% of subjects in the mCC study arm, respectively; and 37.5%, 35.0%, and 15.0% of subjects in the SA arm, respectively.

Analysis of the cough impact scale data (VAS) shows that overall mean VAS was similar during the Confinement Period (from Day 1 to Day 5) in the Safety Population. The mean VAS on Day 1 and Day 5 for the THS 2.2 Menthol and mCC arms was similar suggesting only minor changes over time for these study arms. The mean VAS for the SA arm showed a higher mean VAS on Day 5 (25.5) compared to Day 1 (19.3). In the Ambulatory Period, similar mean VAS on Day 90 were observed compared to Day 5 for the THS 2.2 Menthol and mCC arms. In the SA arm, Day 90 and Day 5 mean VAS values were similar but a peak VAS value was observed on Day 60 for this study arm (40.3).

12.5 Safety Conclusions

There were no SAEs or severe AEs reported in this study and no randomized subjects were discontinued due to an AE. Prior to randomization, 15 subjects were discontinued from the study, of which 2 subjects were discontinued due to an AE. In addition, 56 subjects were



excluded from the Safety and FAS populations due premature termination of the site where subjects were enrolled.

Overall, there were 93 AEs reported post-randomization by 60 of the 160 subjects (37.5%) in the Safety Population, most of which were mild in severity. Only 2 AEs were considered moderate, with 1 moderate AE reported in the Confinement Period for the SA arm and 1 moderate AE reported in the Ambulatory Period for the mCC arm. The number of subjects reporting AEs in each study arm were 32/78 (41.0%) for the THS 2.2 Menthol arm, 14/42 (33.3%) for the mCC arm, and 14/40 (35.0%) for the SA arm.

Only 1 AE reported was considered to be related to the IP. This was diarrhea reported in the THS 2.2 Menthol arm during the Confinement Period and was considered not expected. In addition, 6 AEs were considered related to study procedures, with 4 AEs during the Confinement Period and 2 AEs during the Ambulatory Period.

Overall, the most frequent AEs reported post-randomization by SOC were Investigations, which were experienced by 24/78 subjects (30.8%) in the THS 2.2 Menthol arm, 8/42 subjects (19.0%) in the mCC arm, and 10/40 subjects (25.0%) in the SA arm.

The most frequent AEs by PT reported were decreased hemoglobin, decreased neutrophils, increased blood TGs, and nasopharyngitis, with the majority of incidences occurring for these PTs during the Ambulatory Period. Throughout the study, 11/78 subjects (14.1%) in the THS 2.2 Menthol arm, 3/42 subjects (7.1%) in the mCC arm, and 3/40 subjects (7.5%) in the SA arm experienced decreased hemoglobin (haemoglobin decreased). Overall the proportion of subjects who experienced neutrophil count decreased, blood TG increased, and nasopharyngitis was $\leq 5.0\%$ and the proportions of subjects in each study arm were similar.

Overall, 53 subjects in the THS 2.2 Menthol arm (67.9%) reported a total of 144 major device events or malfunctions; 26 subjects (33.3%) during the Confinement Period and 44 subjects (56.5%) during the Ambulatory Period. None of these events led to an AE.

There were no clinically significant or relevant abnormalities in vital signs, ECG, or spirometry findings.



13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This study was designed to demonstrate the reduction in exposure to selected HPHCs achievable in a 5-day confined setting, and sustainable in an 85-day ambulatory setting, when switching from mCC to THS 2.2 Menthol use, compared to continuing to smoke mCC. Smokers who remained abstinent from smoking were used as a benchmark to provide context to the exposure reduction.

The THS 2.2 Menthol product was primarily designed to be used as an alternative to, and not in combination with mCC. Therefore a PP approach was taken for the primary analysis in this study in order to assess the optimal reduction in exposure to HPHCs in subjects using predominantly THS 2.2 Menthol; the PP Set populations included all subjects randomized, with no major protocol deviations and who were compliant to their allocated product (not more than 2 mCC on any day, and not more than 0.5 mCC on average per day) over the exposure period studied.

The study began with a period of Confinement where mCC and THS 2.2 Menthol product distribution and access was strictly controlled to ensure 5 days of exclusive use of THS 2.2 Menthol or mCC, or continuous abstinence from smoking in the SA arm. An Ambulatory Period of 85 days immediately followed, where subjects were asked to continue to exclusively use their allocated product (THS 2.2 Menthol or mCC) or to continue to abstain from smoking during their daily life (SA). The Confinement Setting investigated the maximum possible exposure reduction to selected HPHCs, whereas, the Ambulatory Setting investigated if the exposure reduction to selected HPHCs observed during the Confinement Period was sustained in a less controlled, more real-life setting.

Furthermore, this study evaluated the adaptation to, and acceptance of THS 2.2 Menthol as a substitute for mCC through the assessment of changes in product use patterns, HST, and subjective effects over time. Finally, a number of CREs representative of pathways involved in the pathogenesis of smoking-related diseases were assessed.

Exposure to Smoke Constituents

In 2012, the US FDA's Center for Tobacco Products established a list of 18 HPHCs recommended to be measured in tobacco smoke [36]. The present study assessed exposure to 16 HPHCs as well as nicotine, including 14 of those requested by the FDA for reporting, including a range of chemical and toxicity classes. Significant and sustainable reductions in the corresponding BoExp levels (except S-BMA) were observed throughout the entire exposure period with 49% to 94% and 41% to 94% reduction on Day 5 and Day 90, respectively, in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. The results observed are a consequence of the heat not burn product design of THS 2.2 Menthol, by which combustion is eliminated and thus,



provides reasonable confidence that THS 2.2 Menthol reduces the exposure to HPHCs beyond the toxicants measured in this study as compared to mCC.

Overall, the magnitude of reduction in exposure to HPHCs was comparable between both the Confinement and Ambulatory Periods, although slightly less pronounced in the Ambulatory Period. Potential confounding factors associated with the “real-life” conditions of the Ambulatory Period and known to affect the levels of BoExp, such as food and environmental air pollution, but also exposure to passive smoking, are likely to best explain such differences.

The reduction observed in the levels of Total NNAL and CEMA in the Ambulatory Period was slightly higher than that observed in the Confinement Period, with reductions of 56.31% on Day 5 and 76.75% on Day 90 for Total NNAL, and reductions of 81.77% on Day 5 and 90.83% on Day 90 for CEMA in the THS 2.2 Menthol arm compared to the mCC arm. In contrast to the other BoExp which exhibit a half-life of approximately 1 to 2 days, the elimination half-lives of Total NNAL is 10 to 18 days for Total NNAL [12]. For CEMA, in contrast to an estimated elimination half-life of 7 hours reported in the literature [37], an analysis derived from a PMI study (ClinicalTrials.gov: NCT01465880) estimated the half-life as approximately 2 days (data on file). As a consequence, the time-to-maximum elimination, expected to be achieved after 4-fold to 5-fold elimination half-life, exceeded the duration of the Confinement Period and most likely explains the greater reduction observed during the Ambulatory Period.

Mean S-BMA (BoExp to toluene) levels were not meaningfully changed across the 3 arms as observed in other BoExp with minimal reductions in the THS 2.2 Menthol and SA arms during the Confinement Period and Ambulatory Period. This further confirmed that, although S-BMA is a suitable BoExp to toluene in environmental and occupational studies [38], its suitability to discriminate between smokers and non-smokers seems questionable. Various studies have reported overlapping ranges in S-BMA levels with only subtle increases observed between smokers and non-smokers [38-40]), which is in agreement with the findings of this study.

The Institute of Medicine refers to smoking cessation as the “gold standard” for assessing risk reduction, and states that “the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit” [6]. This study showed that for most of the BoExp assessed, the magnitude of reduction after switching to THS 2.2 Menthol was comparable or close to levels of BoExp observed in the SA arm. The differences observed for Total NNAL (1.2 to 1.5 higher), 3-HPMA (1.4 to 1.7 higher), and Total NNN (5-fold to 8-fold higher) between the THS 2.2 Menthol arm and the SA arm are likely explained by the residual levels of the corresponding HPHC in the aerosol of THS 2.2 Menthol as evaluated by the smoke chemistry [7]. For 3-HPMA, exposure through sources such as food or other environmental exposure may have played a role. Furthermore, potential endogenous



formation of small amounts of acrolein and its metabolites during the catabolism of various amino acids and polyamines, and metabolic variability in terms of rate and amount of excretion of 3-HPMA may have played a role [4, 41]. The 49% reduction observed in 3-HPMA following the use of THS 2.2 Menthol was smaller than the expected 70% reduction (see Section 9.7.4). However, the THS 2.2 Menthol : SA ratio was 166% on Day 5, close to the anticipated value of 170%, thus suggesting that approximately the expected amount of SA effect was preserved in THS 2.2 Menthol study arm (approximately 70%). Although, higher levels were found between the THS 2.2 Menthol and SA arms for Total NNN, Total NNAL, and 3-HPMA, when analyzed in the context of the reduction from mCC, THS 2.2 Menthol preserved most of the reduction from mCC observed for SA.

Baseline COHb levels were in agreement with the levels found in smokers (Institute of Medicine reports ranges of 3.4% to 7.1% [6] and remained steady in the mCC arm throughout the study, as expected. By contrast, in the THS 2.2 Menthol arm, levels dropped similarly to those of the SA arm as of Day 1, and plateaued thereafter reaching a reduction of 55.06% between THS 2.2 Menthol and mCC after 5 days of product use, and sustained (48.28%) until Day 90. Following 3 months of product use, the COHb levels were similar in the THS 2.2 Menthol and SA arms, with values of 2.96% and 3.05%, respectively. The Agency for Toxic Substances and Disease Registry report that COHb levels $\geq 2.4\%$ may have adverse cardiovascular effects in subjects with compromised cardiovascular function [42]). Similarly, the WHO environmental health criteria 213 on CO states that carboxyhemoglobin level of 2.5% should not be exceeded so as to prevent untoward hypoxic effects on the non-smoking population with coronary artery diseases [43]. Although the recommended levels by the Agency for Toxic Substances and Disease and the WHO were slightly exceeded, this is unlikely to have been due to an effect of THS Menthol 2.2 as levels in the THS Menthol 2.2 arm were comparable to the SA arm. However, environmental exposure to CO might have played a role and could explain this observation.

The sustained reduction in the mutagenic potential of urine in the THS 2.2 Menthol users throughout the study (2.3-fold less compared to baseline following 5 days of THS 2.2 product use and 2.6-fold less compared to baseline following 90 days of product use) compared to the mutagenic potential of urine observed in the mCC users (1.1-fold decrease following 5 days and 1.1-fold increase following 90 days) are likely a direct effect of the achieved sustained exposure reduction when switching from mCC to THS 2.2 Menthol. A decrease in mutagenic potential of urine was apparent in both the THS 2.2 Menthol and SA arms during the exposure period (both the Confinement and Ambulatory Periods). The interpretation of the Ames mutagenicity test including the decrease observed in the mCC arm during the Confinement Period is limited due to the considerable variability of results. These results could be partly explained by the high sensitivity of this test to dietary mutagens, and low selectivity to the sources present in the aerosols [44].



Overall, the study results demonstrated the use of THS 2.2 Menthol to significantly reduce exposure to HPHCs, close to levels observed following SA in this study and comparable to what is reported in the literature [45]. The results of the PP analysis were comparable to the analysis done on the FAS population, as the number of subjects on dual-use was low. In this study, a high level of compliance to product allocation was observed, with more than 80% of subjects being exclusive users of THS 2.2 Menthol product in the THS 2.2 Menthol arm during Period 4 (Days 60 to 90). This study demonstrated that despite the various confounding factors, which may influence the levels of exposure to selected HPHCs, a reduction in exposure was achieved at the end of the Confinement Period and was sustained throughout the Ambulatory Period.

Product Use Assessment

Overall, the average daily THS Menthol Tobacco Stick consumption remained unchanged in the THS 2.2 Menthol arm between product use at baseline and the end of the exposure period. After the lower use of THS Menthol Tobacco Sticks at Day 1 compared to mCC at baseline, consumption of THS Menthol Tobacco Sticks increased from Day 1 to Day 5 followed by a subsequent reduction of product use between Day 5 and Day 30, and only limited change between Day 30 and the end of the Ambulatory Period. A high level of compliance was observed in this study, with more than 82.1% exclusive users (100% use) in the THS 2.2 Menthol arm during Period 4 (Days 60 to 90), and with very limited reported dual-use. The number of mCC smoked daily slightly increased through the course of the study, with approximately a 20% increase from baseline to Day 90 in the mCC arm.

The observed kinetics of nicotine exposure showed an initial drop of nicotine levels from baseline to Day 1 before increasing to levels slightly above baseline on Day 5 with nicotine exposure about 16% higher as compared to subjects who continued to smoke mCC, reaching a steady state from Day 30 onwards. Levels of nicotine for THS 2.2 Menthol and mCC arms at Day 90 however, were similar (4% higher in THS 2.2 Menthol compared to mCC arms). In the mCC arm on Day 90, there was a 25.83% increase from baseline in NEQ likely to result from the 20% increase in the number of mCC smoked on a daily basis compared to baseline. The levels of plasma cotinine confirmed these results and followed similar trends as for urinary NEQs. The changes in nicotine exposure and consumption of THS Menthol Tobacco Sticks over time suggest a transitional adaptation after switching to a new product, with different characteristics, to achieve the levels of nicotine desired by the THS 2.2 Menthol user.

For THS 2.2 Menthol users, this adaptation was also observed in HST parameters, which showed an early initial decrease of total puff volume on Day 1 of approximately 16%, driven by a decrease of average puff volume of about 8% compared to mCC. The total puff volume subsequently increased, reaching a plateau by Day 60, with the levels comparable to what was observed in the mCC arm on Day 90 (-23.47 mL). This adaptation was achieved by subjects increasing their puff frequency and consequently the overall number



of puffs over time. The changes in the HST parameters matched well with the changes in product use and nicotine exposure, and could be used as an indicator of nicotine uptake.

Overall, it is reasonable to conclude that THS 2.2 Menthol users were able to fully adapt to the new product during the Ambulatory Period, titrating and controlling nicotine uptake at a rate compared with mCC, and close to levels measured at baseline when subjects were using their own preferred brand of mCC.

Subjective Effects

Furthermore, this study included endpoints to assess the overall satisfaction and acceptance of THS 2.2 Menthol as a substitute for mCC by smokers.

The mean urge-to-smoke and the withdrawal symptoms scores were similar, stable, and comparable from baseline throughout the entire exposure period for THS 2.2 Menthol and mCC arms. For the SA arm, although the mean urge-to-smoke score expectedly increased from baseline to Day 1, it decreased gradually over the study period, reaching values similar to those observed in the THS 2.2 Menthol and mCC arms by the end of the Ambulatory Period.

Similar results were observed for withdrawal symptom scores using the MNWS-R questionnaire, where no apparent difference between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC was shown. In contrast, and as expected, an initial increase from baseline was evident in the SA arm.

Furthermore, the MCEQ scale showed no notable differences in LS mean differences for psychological reward, smoking satisfaction, aversion, and craving reduction on Day 90 between THS 2.2 Menthol and mCC arms. This was achieved despite the fact that for THS 2.2 Menthol, there was an initial decrease from baseline in mean scores on Day 1 for craving reduction (-8.49%), enjoyment of respiratory tract sensation (-3.41%), psychological reward (-15.77%), and smoking satisfaction (-23.76%), with scores subsequently increasing during the Ambulatory Period reaching scores comparable to mCC within 3 months.

The change in taste, sensorial experience, ritual, and differences in the ISO tar and nicotine yield of THS 2.2 Menthol, are likely reasons for the observed differences in overall satisfaction at the beginning of the exposure period requiring an adaptation to THS 2.2 Menthol over time. However, study results suggest, that subjects successfully adapt over time to the new product and that the THS 2.2 Menthol product was providing similar levels of reduction of urge-to-smoke, satisfaction and enjoyment to that of mCC.



Risk Markers

The disorders induced by smoking CC are complex as there are multiple causal chains and disease develops over many years. Consequently, there is no single CRE that, in and of itself, can be considered as a validated surrogate measure for the spectrum of adverse health effects associated with smoking. The exposure to HPHCs affects multiple organ systems, disease pathways, and mechanisms such as inflammation, oxidative stress, platelet activation and lipid metabolism, which occur simultaneously and cannot be expressed by a single endpoint. Therefore, within these pathways, several CREs that are related to the pathophysiological mechanisms of these smoking-related diseases have been identified. Many of these CREs have been shown to be sensitive to changes in smoking status and favorably change in the short to mid-term (e.g., within one week to one year) following smoking cessation, and thus would indicate a favorable risk profile against which to assess a candidate MRTP, such as THS 2.2 Menthol.

The CREs monitored and expected to be favorably changed when switching to THS 2.2 Menthol use in this study included CREs related to lipid metabolism (i.e., HDL cholesterol), inflammation (i.e., WBC), endothelial dysfunction (i.e., sICAM-1), platelet activation (i.e., 11-DTX-B2), and oxidative stress (i.e., 8-epi-PGF_{2α}), which all play a role and contribute to cardiovascular diseases and/or are markers of disease pathways linked to various other smoking-related diseases. All are reported in the literature to be unfavorably affected by smoking status with these changes being reversible upon smoking cessation [15, 17, 18].

Other CREs such as systolic and diastolic blood pressure, TC, TGs, LDL cholesterol, platelet count, fibrinogen, hs-CRP, homocysteine, HbA1c, waist circumference, and weight were also assessed to provide overall context and comprehensive information on the cardiovascular profile of the subject.

Although FEV₁ was not to be analyzed as a CRE in the protocol, and therefore, the analysis was not planned prior to the database lock, PMI considers FEV₁ to be a CRE with an improvement in lung function reported in the literature upon smoking cessation [46-49]. Therefore, a posthoc analysis was performed for FEV₁ following the same approach as for other CREs.

An increase of 1.91 %predicted (95% CI: -0.14, 3.97) in FEV₁ was observed for the THS 2.2 Menthol arm following 90 days of THS 2.2 Menthol use with no notable difference between THS 2.2 Menthol and SA arm. These data are promising but further studies of longer duration (at least 6 to 12 months) when switching to THS 2.2 Menthol are needed to confirm the initial favorable changes in FEV₁ over time.

Similarly, CREs selected for this study as indicators of the mechanistic pathways related to cardiovascular disease such as HDL cholesterol, 8-epi-PGF_{2α}, 11-DTX-B2, sICAM-1, and WBC count resulted in favorable changes following the trajectory of SA. These data seem



to indicate that the exposure reduction achieved by switching to THS 2.2 Menthol translates into reduced risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol over time.

However, the levels of reduction for 11-DTX-B2 and 8-epi-PGF_{2α} were lower than expected in the THS 2.2 Menthol arm. Natural variability and factors such as age, sex, smoking history, or concomitant medication may explain these results; however, this would need further investigation. It is not excluded that the nicotine delivered by THS 2.2 Menthol may interfere and minimize the favorable changes. Indeed, the decline in the levels of sICAM-1 following smoking cessation was reported to be minimized in subject using nicotine replacement patches as compared to those receiving no treatment [17]. To our knowledge, no data on 11-DTX-B2 and 8-epi-PGF_{2α} are available in the Japanese population upon smoking cessation; however, the lower levels of cardiovascular CREs and the lower incidence of coronary heart diseases reported despite higher smoking rates than in the Japanese population than as compared to Western countries could explain these unexpected results [50]. In consequence, changes in CREs discussed may also require longer periods of switching to THS 2.2 Menthol or SA than the duration of this study allowed, or an increased sample size; although literature on other populations reports favorable changes after at least 2 weeks for 8-epi-PGF_{2α} [18, 51] and for 11-DTX-B2 [52-54].

Overall, the directional shift of CREs in the THS 2.2 Menthol arm towards that observed in the SA arm adds to the clinical relevance of the observed exposure reduction and may indicate that the exposure reduction achieved by switching to THS 2.2 Menthol may translate into biological and functional changes potentially known to be involved in the pathogenesis of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.

CYP1A2 and CYP2A6

The study evaluated the impact of using THS 2.2 Menthol on cytochrome P450 enzymes i.e., CYP1A2 and CYP2A6.

The CYP1A2 enzymes are mono-oxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines, [55]). Cytochrome P450 1A2 also catalyzes many of the reactions involved in the metabolism of low therapeutic-index drugs and synthesis of cholesterol, steroids, and other lipids [56]). The CYP1A2 expression is induced to a large extent by polycyclic aromatic hydrocarbons (PAH) which are found in cigarette smoke [57]).

In this study, CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was reduced to similar levels to those observed in subjects who abstained from smoking and were in line with what is reported in the literature following 5 days of SA [13]). These



results are likely to be linked to the overall reduction of exposure to PAH. The reduction of CYP1A2 was sustained throughout the Ambulatory Period.

Overall, the results are indicative of a reduction in harmful carcinogenic metabolites resulting from a reduced CYP1A2 activity after THS 2.2 Menthol use, similar to what was observed in the SA arm.

The ratio of nicotine metabolite, trans-3'-hydroxycotinine, to cotinine in biological fluids, is an indicator of CYP2A6 activity is highly correlated with the rate of nicotine metabolism, which is catalyzed mainly by cytochrome CYP2A6. In this study, CYP2A6 activity was low in smokers who switched to THS 2.2 Menthol use and comparable to those who maintained mCC use, while activity greatly increased in those who abstained from smoking. The comparable levels of CYP2A6 activity observed in THS 2.2 Menthol users and mCC smokers were expected and can be plausibly explained by the exposure to nicotine, which was similar between the THS 2.2 Menthol and mCC arms in both the Confinement and Ambulatory Periods. Nicotine itself reduces the rate of its own metabolism by inhibiting CYP2A6 activity [52]). The results obtained in the SA arm are in agreement with the literature, where in smokers who were abstinent from smoking for 4 to 7 days the clearance of nicotine was significantly increased compared to smokers [14, 58, 59]).

Safety

There were no SAEs or severe AEs reported in this study and no randomized subjects were discontinued due to an AE. Only 1 AE was assessed as being related to THS 2.2 Menthol or mCC reported in this study; an AE of diarrhea experienced by a subject in the THS 2.2 Menthol arm.

The incidence of subjects experiencing AEs during the study was low, with the majority of AEs mild in severity. The number of AEs and the percentage of subjects reporting AEs exhibited a similar incidence between all study arms. Of those subjects in the THS 2.2 Menthol arm, who were identified as using additional nicotine containing products (5 subjects used electronic cigarettes) approximately 60% (3/5 subjects) reported AEs, compared to 36.6% of exclusive THS 2.2 Menthol users who reported AEs (26/71 subjects).

For subjects enrolled at the Seishukai Clinic, for which AEs have been only listed, there were a total of 14 AEs in 12 subjects following product exposure. None were related to the IP and were all mild in severity.

There were no clinically significant or relevant abnormalities in vital signs, ECG, or spirometry findings.



Strength and Weaknesses of the Study

A strength of the study was that all urinary BoExp were measured in 24-hour urine using validated methods. Compared to partial urine fraction or spot urine, 24-hour collection is considered in the literature to be the most accurate method to assess BoExp. The reduction of each BoExp expressed as quantity excreted showed similar magnitude of reduction as when expressed as concentration adjusted for creatinine. These results showed that potential differences of urinary flow between subjects play a minor role in the excretion of the selected BoExp measured in this study.

In addition, the number and variety of BoExp assessed was another strength of this study. Cigarette smoke is a complex mixture containing more than 6,000 chemical compounds. The assessment of BoExp to HPHCs selected for this study therefore acknowledges that the aerosol/smoke matrix is not amenable to full analytical characterization due to its chemical complexity. Yet, the selected BoExp measured in this study represent HPHCs endorsed by public health authorities as a priority for being reduced in mCC smoke, and are considered by the Institute of Medicine to provide a realistic assessment of human uptake of a variety of toxicants and carcinogens in tobacco products.

The BoExp were selected based on a variety of criteria such as: being (a) specific to the source of exposure with other sources being minor or non-existent, (b) detectable using validated methods, (c) reflecting a specific toxic exposure or a reliable surrogate of exposure to HPHCs, (d) representing a set of HPHCs as listed by the FDA, (e) representing assessment of both gas and particulate phases of the THS 2.2 Menthol aerosol, and (f) covering a broad variety of chemical classes and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, and addiction potential).

Considering the high compliance to product/regimen allocation in the 3 study arms, this study provided robust scientific evidence of optimal exposure reduction when smokers predominantly used THS 2.2 Menthol as an alternative to mCC in comparison to when smokers quit smoking. In addition, the multiple assessments including measurement of nicotine exposure, reporting of daily product use, product satisfaction evaluation together with the human smoking topography, provided a comprehensive understanding of product adaptation and acceptance over the course of the study.

Although promising favorable changes in CREs were observed preserving the majority of the effect of SA, the data obtained on CREs warrants confirmation in longer term studies within larger study populations as the study was not powered to draw definite conclusions.

13.2 Overall Conclusions

The study demonstrated that switching from mCC to THS 2.2 Menthol use in a Japanese smoking population resulted in substantial reductions in exposure to 15 HPHCs, with the



majority of the reduction already achieved after 5 days in Confinement and sustained throughout the 85 days of the Ambulatory Period of the study. The kinetics of the reductions observed for the majority of BoExp in the THS 2.2 Menthol arm were close to that observed in the SA arm, in both the timing and magnitude of the reductions.

The exposure to nicotine in the THS 2.2 Menthol arm initially decreased at Day 1 compared to baseline and further increased from Day 1 to Day 5, reaching a steady state on Day 30. A similar trend was observed in the number of THS Menthol Tobacco Sticks used per day over time. The observed changes in the HST parameters, characterized by an increase in puff frequency and consequently the overall number of puffs over time, correlated well with the changes in product use and nicotine exposure.

While the level of nicotine exposure observed at Day 5 was higher for THS 2.2 Menthol compared to mCC users, the difference between the 2 reduced over time following an increase of daily mCC use during the Ambulatory Period, so that the exposure to nicotine reached a steady state at Day 30 in the THS 2.2 Menthol arm and a continuous increase in nicotine levels in the mCC arm over time. Comparable levels of nicotine exposure were achieved in both arms following 90 days of product use.

In conclusion, the observed kinetics of nicotine exposure, the number of THS Menthol Tobacco Sticks used over time, the observed changes in puffing topography parameters, and the results of subjective effect measures showed comparable results for the THS 2.2 Menthol and the mCC arms from Day 30 onwards. These data suggested that subjects are able to quickly adapt to the THS 2.2 Menthol product, despite the different characteristics respective to their own preferred brand of mCC, by titrating and controlling their desired level of nicotine exposure, and consequently achieving similar satisfaction with the use of THS 2.2 Menthol compared to mCC.

The directional shift of CREs in the THS 2.2 Menthol arm towards SA adds to the clinical relevance of the observed exposure reduction, and may indicate that the exposure reduction attained by switching to THS 2.2 Menthol may translate into biological and functional changes, potentially reducing the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.

There were no SAEs or severe AEs reported in this study and no randomized subjects were discontinued due to an AE. The incidence of subjects experiencing AEs during the study was low, with the majority of AEs mild in severity. The number of AEs and the percentage of subjects reporting AEs exhibited a similar incidence between all study arms.

Overall, the study results demonstrated a sustained exposure reduction to HPHCs after switching to THS 2.2 Menthol in both confined and ambulatory settings, close to levels observed after SA, transforming into favorable changes in CREs, while providing an acceptable alternative to users with regards to taste, ritual, sensorial experience, and nicotine delivery. Therefore, THS 2.2 Menthol might be a suitable substitute for mCC for



adult smokers with the potential to reduce the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.



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15 ADDITIONAL SUMMARIES NOT INCLUDED IN THE TEXT

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- Figure 15.1.1.2 Biomarkers of Exposure Geometric Mean and 95% CI – PP Set
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15.3.4 CYP1A2 Activity Listings

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15.3.5 Ames Mutagenicity Assessment

Listing 15.3.5.1	Listing of Ames Mutagenicity Results and Changes from Baseline
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15.3.6 Safety, Questionnaire, CYP2A6 Activity, and Tobacco Plug Data Listings

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15.3.7 Other Assessments and Comments

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15.4 Statistical Output

15.4.1 Disposition and Background Data

Not applicable.



15.4.2 Product Use

Not applicable.

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- Listing 15.4.3.1.2** Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 and Day 90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective using Mixed Model – PP Set
- Listing 15.4.3.1.3** Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 and Day 90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective – Compliant Population
- Listing 15.4.3.2** Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 and Day 90 Visit for THS 2.2 Menthol versus mCC and SA – PP Set
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- Listing 15.4.3.4** Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5 and Day 90 Visit – PP Set
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- Listing 15.4.4.22.1** Analysis of Plasma Nicotine and Cotinine Concentration PK Parameters on Day 5 – PP Set
- Listing 15.4.4.22.2** Analysis of Plasma Nicotine and Cotinine Concentration PK Parameters on Day 5 – FAS
- Listing 15.4.4.24.1** Analysis of CYP1A2 Activity (%) – PP Set



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- [Listing 15.4.4.24.1.1](#) Analysis of CYP1A2 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP1A2 Activity – PP Set
- [Listing 15.4.4.24.2](#) Analysis of CYP1A2 Activity (%) – FAS
- [Listing 15.4.4.24.2.1](#) Analysis of CYP1A2 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP1A2 Activity – FAS
- [Listing 15.4.4.25.1](#) Analysis of Risk Markers – PP Set
- [Listing 15.4.4.25.1.1](#) Analysis of 11-DTX-B2 (pg/mg creat) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting the Production of 11-DTX-B2 – PP Set
- [Listing 15.4.4.25.2](#) Analysis of Risk Markers – FAS
- [Listing 15.4.4.25.2.1](#) Analysis of 11-DTX-B2 (pg/mg creat) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting the Production of 11-DTX-B2 – FAS
- [Listing 15.4.4.36.1](#) Analysis of QSU-brief Factors and Total Scores – PP Set
- [Listing 15.4.4.36.2](#) Analysis of QSU-brief Factors and Total Scores – FAS
- [Listing 15.4.4.38.1](#) Analysis of MCEQ Subscales – PP Set
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- [Listing 15.4.4.43](#) Analysis of HST Parameters per-Cigarette – PP Set
- [Listing 15.4.4.45.1](#) Analysis of CYP2A6 Activity (%) – PP Set
- [Listing 15.4.4.45.1.1](#) Analysis of CYP2A6 Activity (%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP2A6 Activity – PP Set
- [Listing 15.4.4.45.2](#) Analysis of CYP2A6 Activity (%) – FAS
- [Listing 15.4.4.45.2.1](#) Analysis of CYP2A6 Activity(%) Excluding Assessments within 5 Half-Lives of a Concomitant Medication Affecting CYP2A6 Activity – FAS



16 APPENDICES

16.1 Study Information

16.1.1 Protocol, Protocol Amendments

- 16.1.1.1 Study Protocol (English Language Version)
- 16.1.1.2 Study Protocol (Local Language Version)
- 16.1.1.3 Protocol Amendment No. 1 (English Language Version)
- 16.1.1.4 Protocol Amendment No. 1 (Local Language Version)
- 16.1.1.5 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 Approval, Sample Consent Form, 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
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- 16.1.3.17 IRB Subject Information and Informed Consent Form Version 2.0
Approval Letter Japanese
- 16.1.3.18.1 Subject Information and Informed Consent Form English
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- 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
 - 16.1.6.1 Randomization Scheme and Codes
 - 16.1.6.2 Biostatistical Addendum to IXRS
- 16.1.7 Audit Certificates
- 16.1.8 Documentation of Statistical Methods
 - 16.1.8.1 Statistical Analysis Plan
 - 16.1.8.2 Statistical Posthoc Analysis Plan - Spirometry
 - 16.1.8.3 Statistical Posthoc Analysis Plan - HST (PH02)
- 16.1.9 Bioanalytical Documentation
 - 16.1.9.1 Standardization and Lab 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.

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)

16.5 Not Applicable (US Archival Listings)