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PMI RESEARCH & DEVELOPMENT

# Clinical Study Report

## ZRHM-REXA-08-US

<b>Study Title:</b>	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently 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 86 days in an ambulatory setting
<b>Short Title:</b>	Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting followed by 86 days in an ambulatory setting
<b>Study Number:</b>	ZRHM-REXA-08-US
<b>Product Name:</b>	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
<b>Study Initiated (first subject screened):</b>	17 December 2013
<b>Study Completed (last subject last visit):</b>	12 October 2014
<b>Principal Investigators and Affiliations:</b>	Dr William Lewis, Covance Dallas Site 1341 W. Mockingbird Ln., Suite 400E Dallas, TX 75247 Dr H. Frank Farmer, Covance Daytona Beach Site 1900 Mason Ave., Suite 140 Daytona Beach, FL 32117
<b>Sponsor:</b>	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
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<b>Version:</b>	1.0
<b>Date:</b>	25 May 2016

This study was conducted in accordance with Good Clinical Practice.

### Confidentiality Statement

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

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## SYNOPSIS

<b>Sponsor:</b> Philip Morris Products S.A.	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use only)</b>
<b>Name of Finished Product:</b> Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Not applicable	<b>Page:</b>	
<b>Study Title:</b> A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently 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 86 days in an ambulatory setting		
<b>Principal Investigators and Study Centers:</b> Dr William Lewis, Covance Dallas Site 1341 W. Mockingbird Ln., Suite 400E Dallas, TX 75247  Dr Frank Farmer, Covance Daytona Beach Site 1900 Mason Ave., Suite 140 Daytona Beach, FL 32117		
<b>Publication (reference):</b> ClinicalTrials.gov ID: NCT01989156. Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting followed by 86 days in an ambulatory setting		
<b>Period of Study:</b> First subject screened: 17 December 2013 Last subject last visit: 12 October 2014		
<b>Objectives and Endpoints:</b> <b>Primary Objectives and Endpoints:</b> The primary objectives and endpoints of this study were: <ol style="list-style-type: none"><li>To demonstrate the reduction of primary biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) (except Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [Total NNAL]) in a confinement setting in smokers switching from menthol conventional cigarettes (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.</li></ol> <u>Endpoints</u> <ul style="list-style-type: none"><li>Monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine) in 24-hour urine, and carboxyhemoglobin (COHb) in blood (expressed as % of saturation of hemoglobin) as measured on Day 5.</li></ul> <ol style="list-style-type: none"><li>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.</li></ol> <u>Endpoints</u> <ul style="list-style-type: none"><li>Total NNAL level (concentration adjusted for creatinine) in 24-hour urine fraction as measured on Day 90 Visit.</li></ul>		

**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).

Endpoints

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

Endpoints

- BoExp listed as secondary (expressed as quantity excreted or concentration adjusted for creatinine) as measured in 24-hour urine on Day 5 and on 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.
    - 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) 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, and 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 concentration ( $t_{peak}$ , 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.

#### Endpoints

- Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5 and Day 90 Visit.
7. To determine the changes in lung functions in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

#### Endpoints

- Full lung functions: Diffusion capacity for lung CO (DLCO), rate constant of CO (KCO), forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC), vital capacity (VC) expressed as liters (L), total lung capacity (TLC), forced residual volume (FRV), inspiratory capacity (IC), mid expiratory flow (MEF 25-75).
8. 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.
  - Electrocardiogram (ECG).
  - Clinical chemistry, hematology, and urinalysis safety panel.
  - Physical examination.
  - Concomitant medications.
9. 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/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Highly sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), 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.
- Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) in serum on Day 90 Visit.
- Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6/Discharge Confinement, on Day 30 Visit, Day 60 Visit and Day 90 Visit.
- White blood cell (WBC; leukocytes) and platelet count in blood on Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-prostaglandin F<sub>2α</sub> (8-epi-PGF<sub>2α</sub>) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5 and on 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.

#### **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.

Screening Period: Day -30 to Day -3:

The Screening Period covered 4 weeks (Day -30 to Day -3) prior to Admission to the clinic (Day -2). A demonstration of the THS 2.2 Menthol 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 only performed after 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 THS 2.2 Menthol were enrolled.

All subjects who participated 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 preferred brand of mCC, and baseline values were recorded.

A 4-hour urine fraction was collected on Day -1. On Day 0, 24-hour urine was collected starting in the morning and ending 24 hours later on Day 1, prior to the randomized Exposure Period.

On Day 0, subjects were randomized to 1 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 Screening Visit (stratification factors).

Subjects were informed of their randomized study arm by the study site staff 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]; 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 used their assigned product *ad libitum*. Subjects allocated to the SA arm were asked to abstain from smoking. Subjects in the SA arm were provided psychological support but were not provided with smoking cessation medications. Product use from Day 1 to Day 5 was allowed between 06:30 AM and 11:00 PM. On Day 6, product use was allowed from 06:30 AM onwards. Use of any tobacco/nicotine-containing product other than the assigned product/regimen was not allowed during Confinement.

Twenty-four-hour urine was collected from Day 1 to Day 5 on site.

Exposure Period in Ambulatory Setting: Discharge on Day 6 until Discharge on Day 91:

At Discharge on Day 6, subjects were instructed to continue their assigned product/regimen in an ambulatory setting for 86 days. All subjects in the SA arm received smoking cessation counseling and were able 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 Ambulatory Visit covered 2 consecutive days on site. For each Ambulatory Visit, the subject checked in in the morning prior to 08:30 AM, and checked out the next day. Twenty-four-hour urine was collected at each Ambulatory Visit starting in the morning from 09:00 AM, with the sample collection spanning 2 days. For the Day 90 Visit, urine was collected from 09:00 AM on Day 90 and the end of the 24-hour urine collection ended in the morning of Day 91, which was subsequently followed by



the collection of a 4-hour urine fraction.

Product use during Ambulatory Visits was unrestricted, and subjects in the THS 2.2 Menthol and mCC arms were allowed to use their assigned product from the time of check-in in the morning, prior to 08:30 AM, until around 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. On Day 91/Discharge Ambulatory, subjects were allowed to use their own mCCs after all safety examination procedures had been conducted. Subjects were then subsequently discharged from the investigational site.

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

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 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 with a limited degree of blinding up to the data review and in the decision of 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
<b>Screened:</b>	<b>659 subjects</b>
Subjects excluded and not exposed to THS 2.2 Menthol	494 subjects
Subjects exposed to THS 2.2 Menthol:	165 subjects
<b>Safety Population:</b>	<b>165 subjects</b>
<b>Exposed and not enrolled</b>	<b>1 subject</b>
<b>Enrolled</b>	<b>164 subjects</b>
<b>Randomized</b>	<b>160 subjects</b>
<b>Full Analysis Set (FAS) population:</b>	<b>160 subjects</b>
<u>Per Protocol (PP) Set:</u>	
PP Set Period 1:	134 subjects
PP Set Period 2:	87 subjects
PP Set Period 3:	86 subjects
PP Set Period 4:	88 subjects
<u>Compliant populations:</u>	
Compliant Population Period 1	134 subjects
Compliant Population Period 2:	74 subjects
Compliant Population Period 3:	77 subjects
Compliant Population Period 4:	79 subjects

**Diagnosis and Main Criteria for Inclusion:**

One hundred and sixty female or male smoking healthy subjects, who met the following main inclusion criteria were planned to be randomized:

- Subject had signed the informed consent form (ICF) and was able to understand the information provided in the Subject Information Sheet and ICF.
- Subject was at a minimum 22 years of age.
- Smoking, apparently 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, vital signs, physical examination, ECG, chest X-ray, and medical history).



- Subject smoked at least 10 commercially available mCCs per day (no brand restrictions), 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  $\geq 200$  ng/mL).
- The subject did not plan to quit smoking within the next 6 months as assessed by the Prochaska 'Stage of Change' questionnaire.
- The subject was ready to comply with the study protocol (e.g., readiness to accept interruptions of smoking for up to 91 days and to use THS 2.2 Menthol). Readiness to use THS 2.2 Menthol was asked on Day of Admission after the product test.

Some specific exclusion criteria for the study were:

- Subject who had  $FEV_1/FVC < 0.7$  and  $FEV_1 < 80\%$  predicted value at post-bronchodilator spirometry.
- Subject with asthma condition ( $FEV_1/FVC < 0.75$  and reversibility in  $FEV_1 > 12\%$  [or  $> 200$  mL] from pre- to post-bronchodilator values).

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

**Test Product and Lot Numbers:**

THS 2.2 Menthol 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 packed THS Menthol Tobacco Sticks: B-08545. Production date: 28 October 2013; Expiry dates: 27 July 2014 and 27 November 2014.

**Duration of Exposure Period:**

The randomized Exposure Period was approximately 91 days and was from Day 1, 06:30 AM until Discharge on Day 91. The Exposure Period included both exposure during the Confinement and 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 brand of mCC. Smoking abstinence was included in this study as a reference point.

**Statistical Methods:****Data Set Populations:**

The PP Set was the primary analysis set for BoExp, CREs, and questionnaire assessments. The FAS was the primary analysis set for compliance to randomization arm. 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. Summaries of the extent of exposure were produced for the FAS and PP Set.

**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, and S-PMA (each adjusted for creatinine) in 24-hour urine, and COHb in blood (expressed as % of saturation of hemoglobin), as measured on Day 5. 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 assessed on Day 90.

The endpoints included in the primary objectives were log-transformed ( $\text{base}_e$ ) 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, estimate of the difference, and its 2-sided 95% confidence intervals (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 reported in the tables. 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, 95% CI, median, first and third quartiles, minimum, and maximum; for log-normal data the geometric mean, geometric 95% CI, and geometric coefficient of variation were also presented for each study arm. In addition, BoExp for the endpoints related to the primary objectives were summarized, stratified by sex and mCC consumption, for the PP Set.

#### Secondary Analyses:

The BoExp included as endpoints in the primary objective were analyzed in the secondary objectives on 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 secondary endpoints were exhaled CO and Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (Total 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 as for the primary analyses. Carbon monoxide was analyzed on the linear scale and arithmetic means were calculated; whereas other BoExp were analyzed to calculate geometric means from the logarithmic scale. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value  $\leq 0.025$ ) 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 presented in the tables (for exhaled CO, the difference in LS means and 95% CI were presented).

Biomarkers of exposure were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as above.

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 presented in the tables. All figures, summaries, and analyses were performed on the PP Set and FAS.

The peak nicotine and cotinine plasma concentration ( $C_{peak}$ ) and  $t_{peak}$  were obtained directly from the plasma concentrations taken on Day 5. If the peak concentration occurred at more than one time point then  $t_{peak}$  was assigned to the first value. The weighted average plasma concentration over 24 hours on Day 5 ( $C_{avg}$ ) was calculated by dividing the area under the curve from 0 to 24 h ( $AUC_{0-24 h}$ ) by 24, where the  $AUC_{0-24 h}$  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 on 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 the 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 CC, THS Menthol Tobacco Sticks) was recorded in the electronic diary 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. An ANOVA model was used as described above for the nicotine and cotinine PK parameters. No adjustments were made for multiple comparisons. If the results from the Day 5 analysis were significant (one-sided p-value  $\leq 0.025$ ) 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 presented in the tables. All CYP1A2 summaries and analyses were performed on the FAS and PP Set as above.

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

The analysis compared the results on Day 90 between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms. An ANCOVA model was used with terms for baseline result, stratification factors, and randomization arm. If 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 presented. All CRE summaries and analyses were performed on the PP Set and the FAS.

Product preference was summarized by randomization arm using the product which the subject preferred to be randomized to (THS 2.2 Menthol, mCC, SA or No preference).

Least squares means for each human smoking topography (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 levels 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 the 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 on Day 5 then the endpoint was further tested on 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 at the Day 90 Visit 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:**

Adverse events (including SAEs and AEs that lead to discontinuation) were summarized by study arm and product exposure for the Safety Population. Adverse events were categorized by system organ class 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), full lung function, ECG data, clinical laboratory safety parameters (clinical chemistry, hematology, and urinalysis), body mass index, physical examination, and device malfunction/misuse events were summarized.

All medications were listed by actual exposure 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.

Although full lung function data was specified to be analyzed by the Safety Population in the Statistical Analysis Plan (SAP), this was an oversight as the original intent for these data was to analyze them as a secondary (efficacy) endpoint, and so posthoc analysis was performed using a mixed model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

## Summary of Results

### Primary Objectives and Endpoint Analyses

The primary objectives for this study were assessed on Day 5 for the BoExp COHb (expressed as % saturation of hemoglobin); and for the following urinary BoExp expressed as urinary concentration adjusted for creatinine: MHBMA (pg/mg creat); 3-HPMA (ng/mg creat); and S-PMA (pg/mg creat); and on Day 90 for urinary Total NNAL expressed as urinary concentration adjusted for creatinine (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 62% (95% CI: 57.5, 65.8) in COHb, 87% (95% CI: 83.0, 90.7) in MHBMA, 54% (95% CI: 46.6, 60.8) in 3-HPMA, and 87% (95% CI: 83.4, 90.5) in S-PMA. In addition, on Day 90, a reduction of 74% (95% CI: 59.7, 82.7) 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 greater than 50% reduction in smokers that switched to THS 2.2 Menthol compared to smokers that continued to smoke mCC.

### 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	Geometric LS Mean Ratio (THS m2.2:mCC)		Geometric LS Mean Ratio (THS m2.2:SA)	
	(%)	95% CI	(%)	95% CI
Evening COHb (%)				
Day 5	38.14	34.24, 42.47	97.30	86.02, 110.05
Day 90	46.76	39.75, 55.00	90.50	69.88, 117.19
Urinary MHBMA (pg/mg creat)				
Day 5	12.58	9.27, 17.05	116.84	83.12, 164.24
Day 90	18.52	12.85, 26.67	64.77	36.88, 113.74
Urinary 3-HPMA (ng/mg creat)				
Day 5	45.77	39.22, 53.41	182.92	153.51, 217.97
Day 90	52.02	40.80, 66.33	147.34	101.23, 214.45
Urinary S-PMA (pg/mg creat)				



Day 5	12.58	9.54, 16.58	102.34	74.82, 139.37
Day 90	22.08	13.52, 36.06	117.51	55.32, 249.57
Urinary Total NNAL (pg/mg creat)				
Day 5	43.81	36.92, 51.97	99.99	82.32, 121.44
Day 90	26.41	17.31, 40.26	75.98	39.92, 144.61
Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; 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.				

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 maintained during the Ambulatory Period, with decreases of 53% in COHb, 81% in MHBMA, 48% in 3-HPMA, and 78% in S-PMA, evident on Day 90. In addition, the initial reductions in levels of Total NNAL observed on Day 5 (56%) further decreased until Day 90 (74%) 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, S-PMA, and Total NNAL.

The level of 3-HPMA was 83% higher on Day 5 and 47% higher on Day 90 for the THS 2.2 Menthol arm compared to the SA arm. 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.

*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	Geometric LS Mean Ratio (THS m2.2:mCC)		Geometric LS Mean Ratio (THS m2.2:SA)	
	(%)	95% CI	(%)	95% CI
Urinary Total 1-OHP (pg/mg creat)				
Day 5	48.11	42.11, 54.96	104.96	90.17, 122.16
Day 90	66.46	52.67, 83.84	114.73	79.83, 164.88
Urinary Total NNN (pg/mg creat)				
Day 5	14.06	10.38, 19.06	678.32	479.07, 960.44
Day 90	17.80	12.31, 25.75	268.55	153.11, 471.04
Urinary 4-ABP (pg/mg creat)				
Day 5	19.31	14.90, 25.01	120.62	89.83, 161.97
Day 90	28.48	19.51, 41.58	101.66	56.81, 181.90
Urinary 1-NA (pg/mg creat)				
Day 5	4.15	3.28, 5.25	116.96	89.59, 152.70
Day 90	14.29	9.47, 21.56	133.95	71.10, 252.34
Urinary 2-NA (pg/mg creat)				
Day 5	13.12	10.49, 16.40	109.03	84.55, 140.59
Day 90	16.04	11.87, 21.67	83.61	52.57, 132.97



Urinary o-toluidine (pg/mg creat)				
Day 5	48.72	39.70, 59.79	128.72	102.10, 162.28
Day 90	43.29	32.00, 58.55	112.05	70.79, 177.37
Urinary CEMA (ng/mg creat)				
Day 5	17.23	14.44, 20.55	105.84	86.65, 129.27
Day 90	14.29	9.01, 22.67	82.18	40.63, 166.22
Urinary HEMA (pg/mg creat)				
Day 5	39.19	31.22, 49.20	104.63	80.79, 135.51
Day 90	38.49	28.28, 52.38	77.74	48.68, 124.14
Urinary B[a]P (fg/mg creat)				
Day 5	28.94	23.14, 36.20	152.32	116.94, 198.39
Day 90	43.33	31.52, 59.57	92.93	57.11, 151.22
Urinary HMPMA (ng/mg creat)				
Day 5	38.26	30.73, 47.64	120.95	94.28, 155.18
Day 90	49.63	37.25, 66.13	102.41	66.08, 158.69
Urinary S-BMA (pg/mg creat)				
Day 5	116.05	90.29, 149.14	81.01	60.97, 107.63
Day 90	109.86	75.25, 160.39	88.13	49.39, 157.24
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; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic 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 -19.96 (-21.62, -18.31) versus mCC and 0.17 (-1.72, 2.07) versus SA; Day 90 -14.62 (-17.67, -11.57) versus mCC and -0.10 (-4.99, 4.78) versus SA.				

Reductions observed in the THS 2.2 Menthol arm compared to the mCC arm (excluding S-BMA) ranged from 34% (Total 1-OHP) to 96% (1-NA) on Days 5 and 90.

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 higher in the THS 2.2 Menthol arm compared to the SA arm on Day 5 and Day 90. However, the numerical values for both the THS 2.2 Menthol and SA arms were very low, i.e., within the range of 0.91 and 0.13 pg/mg creat respectively, and the majority of the decrease of the SA arms was preserved in THS 2.2 Menthol.

Levels of S-BMA on Day 90 were comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued smoking mCC or 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 from baseline to Day 2 (-21.27%), and then increased from Day 3 to Day 5, up to Day 30 (6.60%), with NEQ levels similar to baseline on Days 60 and 90 (-1.39% and -3.86%, respectively).

On Day 5, NEQ urinary concentration adjusted for creatinine was 13% lower in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC (95% CI: -8.2, 29.5). 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 (96% geometric mean ratio; 95% CI: 66.4, 139.6).





A similar trend was observed for nicotine and cotinine concentrations in plasma. On Day 5, the levels of nicotine and cotinine at between 08:00 AM and 09:30 PM were 20% and 16% lower, respectively, in the THS 2.2 Menthol arm compared to the mCC arm (95% CI: 3.4, 34.3 for nicotine; and 95% CI: 1.8, 28.0 for cotinine). These differences decreased over time, starting from Day 30 for both nicotine and cotinine. On Day 90, plasma nicotine and cotinine concentrations were approximately 28% lower and 3% higher, respectively, in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, with 95% CIs spanning 100%. For the nicotine PK profile on Day 5,  $C_{peak}$  and weighted average concentrations were 11% (95% CI: -8.5, 26.3; 20.96 ng/mL for THS 2.2 Menthol arm and 23.43 ng/mL for the mCC arm) lower and 15% (95% CI: -5.6, 31.3; 11.05 ng/mL for THS 2.2 Menthol arm and 12.97 ng/mL for the mCC arm) lower, respectively 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 15% (95% CI: -2.7, 29.1; 217.64 ng/mL for THS 2.2 Menthol arm and 254.96 ng/mL for the mCC arm) and 18% (95% CI: -0.9, 34.1; 189.00 ng/mL for THS 2.2 Menthol arm and 231.72 ng/mL for the mCC arm) lower, respectively, for the THS 2.2 Menthol arm compared to the mCC arm. The median  $t_{peak}$  on Day 5 was similar for the THS 2.2 Menthol and mCC arms for both nicotine (14.97 versus 13.03 hours, respectively) and cotinine (16 hours for both arms).

#### Cytochrome P450 1A2 Activity

On Day 5, CYP1A2 activity had decreased from baseline by approximately 33% and 35% in the THS 2.2 Menthol and SA arms, respectively; while in the mCC arm, CYP1A2 activity had increased from baseline by approximately 4%. During the Ambulatory Period, CYP1A2 activity remained decreased with a 32% and 35% change from baseline in the THS 2.2 Menthol and SA arms, respectively, and a decrease from baseline in the mCC arm of 17% on Day 90.

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 36% (95% CI: 30.8, 41.7) lower than subjects who continued to smoke mCC on Day 5 and 21% lower (95% CI: 7.0, 33.6) 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: 92.1, 111.9 on Day 5; 105%; 95% CI: 80.5, 137.9 on Day 90).

#### Extent of Exposure – Product Use Consumption

During the Confinement Period, for the PP Sets, at baseline (Day 0) the mean number of mCC consumed daily in the THS 2.2 Menthol and mCC arms (Period 1) was 12.2 (95% CI: 11.3, 13.1) and 12.2 (95% CI: 11.1, 13.3) cigarettes/day, respectively. During the Confinement Period, the number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm increased from a mean of 12.5 (95% CI: 11.4, 13.6) sticks/day on Day 1 to 16.5 (95% CI: 15.1, 17.9) sticks/day on Day 5. The mean number of mCC consumed daily was stable throughout the Confinement Period at 11.3 (95% CI: 10.1, 12.5) to 13.7 (95% CI: 12.2, 15.1) sticks/day on Day 1 and Day 5, respectively.

During the Ambulatory Period, for the PP Sets, the mean number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm was lower than Day 5 but higher than the number of mCC/CC consumed at baseline, with a mean 14.7 (95% CI: 12.8, 16.7), 15.2 (95% CI: 12.9, 17.4), and 14.2 (95% CI: 12.1, 16.3) sticks/day reported during Periods 2, 3, and 4, respectively. In the mCC arm, the mean number of mCC/CC consumed daily during the Ambulatory Period remained higher than consumed at baseline, with a mean 15.5 mCC/day (95% CI: 13.4, 17.7) reported during Period 4. For each product use period in the Ambulatory Period, the mean reported daily number of THS Menthol Tobacco Sticks was slightly lower than the daily product use in the mCC arm.

For both the Safety Population and the PP Sets, during the Ambulatory Period the number of THS Menthol Tobacco Sticks used in the THS 2.2 Menthol arm and number of mCC/CC used in the mCC arm was relatively stable. The average reported daily number of THS Menthol Tobacco Sticks used in the THS 2.2 Menthol arm was higher in the PP Set across the Ambulatory Visits (14.2 to 15.2 sticks/day) compared to the Safety Population (11.7 to 12.9 sticks/day), and was comparable to the average daily number of mCC/CC used in the Safety Population (15.0 to 15.8 sticks/day) and PP Set (14.9 to 15.5 sticks/day) for the mCC arm.

Compliance to Investigational Product and Product Use

Compliance to arm allocation was calculated for the PP Sets. During Confinement, full compliance was examined for the THS 2.2 Menthol and mCC arms based on the product distribution log. Five subjects in the THS 2.2 Menthol arm and 6 subjects in the mCC arm were excluded from the PP Set Population during the Confinement due to major deviations including misrandomization. Out of the 75 subjects in the THS 2.2 Menthol arm and 35 subjects in the mCC arm in the PP Set Population, all were exclusively using their allocated product during Confinement. For subjects in the SA arm, the abstinence during Confinement was verified daily using an exhaled CO breath test: Of 39 subjects in the SA arm, 6 subjects had CO breath test above 10 ppm, the cut-off point used to assess SA; all but 1 value above 10 ppm occurred on Day 6 and were excluded from the PP Set Population; 24 subjects had no CO breath test value above 10 ppm after Day 1 during Confinement.

During the Ambulatory Period, full compliance was examined for THS 2.2 Menthol and mCC arms based on product consumption as recorded in their electronic diary. Thirty-two, 36, and 41 subjects in Periods 2, 3, and 4, respectively, for THS 2.2 Menthol arm were exclusively using THS 2.2 Menthol. One subject in the mCC arm was using another product in addition to mCC/CC during Periods 3 and 4. All other subjects were exclusively using mCC/CC during the Ambulatory Period. For subjects in the SA arm, the abstinence during the Ambulatory Period was verified daily based on product consumption as recorded in their electronic diary and verified chemically using an exhaled CO breath test on Day 30, Day 60, and Day 90 Visits. The cut-off point for the CO breath test value for abstinence was 10 ppm. Eight, 7, and 7 subjects in Periods 2, 3 and 4 were categorized as fully abstinent.

Risk markers (Clinical Risk Markers; CREs)

- *Risk Marker of Oxidative Stress: 8-epi-PGF<sub>2α</sub> (Concentration Adjusted for Creatinine) (Day 90)*

The levels of 8-epi-PGF<sub>2α</sub> in subjects who switched to THS 2.2 Menthol were 14% (95% CI: 2.0, 23.6) 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 (geometric mean ratio: 95%; 95% CI: 77.7, 115.1).

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

There were no notable differences in levels of 11-DTX-B2 between subjects who switched to THS 2.2 Menthol and those who continued to smoke mCC (96% ratio; 95% CI: 75.4, 123.3) and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking (geometric mean ratio 104%; 95% CI: 70.4, 153.2).

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

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol were 11% (95% CI: 4.0, 16.7) lower than those 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 (geometric mean ratio 99%; 95% CI: 88.7, 111.1).

- *Risk Markers of Lipid Metabolism: HDL Cholesterol (HDL-C), LDL Cholesterol (LDL-C), Triglycerides (TG), and Total Cholesterol (TC), Apolipoprotein (Apo) A1 and B (Day 90 or Day 91/Day of Discharge from the Ambulatory Period)*

There were no notable differences observed in the levels of HDL-C (1.37 difference; 95% CI: -2.26, 5.00), LDL-C (-3.31 difference; 95% CI: -11.96, 5.34), TC (-4.05 difference; 95% CI: -13.29, 5.19), Apo A1 (3.05 difference; 95% CI: -4.57, 10.67), and Apo B (-1.60 difference; 95% CI: -7.24, 4.03) as well as TG (0.89 difference; 95% CI: -12.72, 14.51) between subjects who switched to THS 2.2 Menthol use, subjects who continued to smoke mCC, and to subjects who abstained from smoking.

- *Risk Markers of Inflammation: Platelets and White Blood Cell (WBC; leukocytes) Differential Counts (Day 91/Day of Discharge from the Ambulatory Period)*

The ratios of platelet counts between subjects who switched to THS 2.2 Menthol use and subjects who





continued to smoke mCC (geometric mean ratio 103%; 95% CI 96.3, 111.2), and as well as subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking (geometric mean ratio 102%; 95% CI: 91.1, 114.5) remained comparable over the study period.

There were no notable differences observed in the total WBC (leukocytes) counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (0.2 GI/L increase with THS 2.2 Menthol compared to mCC; 95% CI: -0.5, 0.8). Total WBC (leukocytes) count was higher by 1.1 GI/L for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.1, 2.2).

Similarly no notable differences were observed in neutrophil levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (0.0 GI/L difference; 95% CI: -0.5, 0.6). Neutrophil levels were higher by 1.0 GI/L for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.2, 1.9).

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, hs-CRP, and fibrinogen, the levels observed between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and subjects who abstained from smoking remained similar.

- *Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure (Day 91/Day of Discharge from the 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, Hemoglobin A1c, Body Weight, and Waist Circumference (Day 90 or Day 91/Day of Discharge from the Ambulatory Period)*

For subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC as well as between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking, levels observed remained similar.

- *Risk Markers for Respiratory Diseases: Lung Function*

In the PP Set (Period 4), there were no notable differences on Day 91/Discharge Ambulatory in gas transfer parameter (DLCO and KCO), lung volume parameters (FRV, TLC, and IC), or spirometry parameters (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and MEF 25-75) between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. On Day 91/Discharge Ambulatory, VC was 0.1 L higher in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC (95% CI: 0.0, 0.2).

Based on 7 to 9 subjects available for analyses in the SA arm, there were no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at both Day 6/Discharge Confinement and Day 91/Discharge Ambulatory in all lung function parameters, except for FRV and IC which were 0.5 L (95% CI: 0.1, 0.8) lower and 0.9 L (95% CI: 0.4, 1.3) higher on Day 91/Discharge Ambulatory in subjects who switched to THS 2.2 Menthol compared to subjects who abstained from smoking.

**Exploratory Endpoint: Product Evaluation Questionnaire (MCEO)**

Craving reduction (THS m2.2 – mCC difference: -1.1; 95% CI: -1.8, -0.4), enjoyment of respiratory tract sensation (difference: -0.6; 95% CI: -1.3, 0.1), and smoking satisfaction (difference: -1.0; 95% CI: -1.5, -0.4) were all lower for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC.



Difference Between THS 2.2 Menthol and mCC Scores for MCEQ Subscales – PP Set		
MCEQ Subscale/Time point	Difference THS 2.2 Menthol - mCC	
	Difference	95% CI
Aversion		
Day 1	-0.10	-0.47, 0.28
Day 5	0.15	-0.20, 0.49
Day 90	0.08	-0.18, 0.34
Craving reduction		
Day 1	-1.6	-2.3, -0.9
Day 5	-1.1	-1.8, -0.4
Day 90	-0.7	-1.4, 0.0
Enjoyment of respiratory tract sensation		
Day 1	-1.1	-1.7, -0.4
Day 5	-0.6	-1.3, 0.1
Day 90	-0.2	-0.8, 0.5
Psychological reward		
Day 1	-0.91	-1.38, -0.45
Day 5	-0.40	-0.86, 0.06
Day 90	-0.30	-0.78, 0.17
Smoking satisfaction		
Day 1	-1.46	-2.03, -0.89
Day 5	-0.96	-1.50, -0.42
Day 90	-0.37	-0.88, 0.13
Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol.		

Over the course of the study, these differences between the THS 2.2 Menthol and mCC arms for the craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction subscales reduced so that there were no notable differences observed for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (difference of 0.1 [95% CI: -0.2, 0.3] for aversion; difference of -0.2 [95% CI: -0.8, 0.5] for enjoyment of respiratory tract sensation; and difference of -0.4 [95% CI: -0.9, 0.1] for smoking satisfaction MCEQ subscales). Craving reduction was still notably lower on Day 90 but less of a difference than on Day 5 (THS m2.2 – mCC difference: -0.7; 95% CI: -1.4, 0.0).

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 the aversion and psychological reward subscales.

**Exploratory Endpoint: Human Smoking Topography (HST)**

Total puff volume for the THS 2.2 Menthol arm increased from baseline to Day 1 and reached its maximum on Day 4, in contrast to what was observed for mCC. This was mainly driven by an increase of average puff volume and the total number of puffs. The THS 2.2 Menthol versus mCC total puff volume exhibited a difference of approximately 187 mL at Day 4. The total puff volume subsequently decreased during the Ambulatory Period in the THS 2.2 Menthol arm. However a similar decrease was observed in the mCC arm eventually resulting in a THS 2.2 Menthol and mCC volume of 792.98 mL and 623.15 mL, respectively, in subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (169.84 mL difference; 95% CI: -69.94, 409.61).



Average puff volume and average puff duration was comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with a 0.12 mL (95% CI: -11.29, 11.05) and 0.32 mL (95% CI: -0.08, 0.71) difference, respectively. In contrast, average flow was 7.41 mL/s lower in subjects who continued to smoke mCC (95% CI: 1.65, 13.18).

The THS 2.2 Menthol users increased the total number of puffs compared to subjects in the mCC arm (3.34 puffs difference; 95% CI: 0.13, 6.81). The total smoking duration was approximately 1.5 minutes lower for subjects who switched to smoking THS 2.2 Menthol compared to subjects who continued to smoke mCC (-88.62 s difference; 95% CI: -146.88, -30.36) while an increase in puff frequency of 2.22 puffs/min (95% CI: 0.55, 3.90) was observed in subjects using THS 2.2 Menthol in comparison with subjects who continued to smoke mCC. These changes were the result of a process of adaptation following the switch to THS 2.2 Menthol.

**Safety:**

There were no SAEs reported by any randomized subject in this study and no randomized subjects were discontinued due to an AE. Prior to randomization, 4 subjects were discontinued from the study, of which 2 subjects were discontinued due to an AE. One subject reported 2 SAEs which were not related to the investigational product (IP) or study procedures and led to the discontinuation of the subject from the study.

Overall, there were 195 AEs reported post-randomization by 95 of the 160 subjects (59.4%) in the randomized Safety Population, most of which were mild or moderate in severity. Twelve severe AEs were reported during the Ambulatory Period, all of which were due to abnormal clinical laboratory findings and were unrelated to IP or study procedures.

The incidence of post-randomization AEs was comparable in the THS 2.2 Menthol arm (52 of 80 subjects [65.0%]) and the SA arm (23 of 39 subjects [59.0%]), and slightly lower in the mCC arm (20 of 41 subjects [48.8%]). Similarly, the frequency of AEs was comparable in the THS 2.2 Menthol arm (114 AEs from 80 subjects) and the SA arm (49 AEs from 39 subjects), and slightly lower in the mCC arm (32 AEs from 41 subjects).

There were 6 AEs reported which were considered to be related to the IP during the Confinement Period, and 2 AEs which were considered to be related in the Ambulatory Period. Seven AEs were considered as related to study procedures, with 6 occurring during the Confinement Period and 1 during the Ambulatory Period.

The most frequent AEs by PT reported were decreased hemoglobin, increased lymphocyte count, upper respiratory tract infection, and headache with the majority of incidences occurring for these PTs during the Ambulatory Period. Throughout the study, 11/80 subjects (13.8%) in the THS 2.2 Menthol arm, 4/41 subjects (9.8%) in the mCC arm, and 6/39 subjects (15.4%) in the SA arm experienced decreased hemoglobin (haemoglobin decreased). The proportion of subjects who experienced increased lymphocyte count, upper respiratory tract infection, and headache was <10% of the subjects in each study arm.

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

There was no safety relevant change in lung function in any study arm during the course of the study.

Overall, 55 subjects in the THS 2.2 Menthol arm (68.8%) reported a total of 149 device events or malfunctions; 27 subjects (33.8%) during Confinement and 46 subjects (57.5%) during the Ambulatory Period. None of these events led to an AE.



**CONCLUSIONS**

The study demonstrated that switching from mCC smoking to THS 2.2 Menthol use resulted in substantial reductions in exposure to assessed HPHCs, with the majority of the reduction achieved after 5 days in Confinement and sustained throughout the 86 days of the Ambulatory Period of the study, while maintaining comparable levels of nicotine. The kinetics of the reductions observed for the majority of BoExp levels in the THS 2.2 Menthol arm were similar to those observed in the SA arm, in both the timing and magnitude of the reductions.

Exposure to nicotine decreased from baseline to Day 2 before rising to levels similar to baseline on Day 30 and was comparable to levels observed in subjects who continued to smoke mCC. The levels of nicotine observed for THS 2.2 Menthol and mCC declined slightly afterwards with comparable levels for both the THS 2.2 Menthol and mCC arms on Day 90.

Most likely driven by the initial decrease in nicotine exposure, product use consumption initially increased in average unit consumption from baseline 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 Exposure Period.

Similarly, total puff volume initially increased from baseline in the THS 2.2 Menthol arm reaching its maximum on Day 4. This was mainly driven by an increase of average puff volume and the total number of puffs. The total puff volume subsequently decreased during the Ambulatory Period in the THS 2.2 Menthol arm; however, a similar decrease was observed in the mCC arm too, resulting in a consistent difference in total puff volume from Day 4 to Day 90 between the THS 2.2 Menthol and mCC study arms.

The initial increase in product use, partially sustained through the Ambulatory Period, together with the immediate increase in total puff volume, were most likely the result of an adaptation process engaged by users to achieve the levels of nicotine desired when switching to a new product which has different characteristics and a lower nicotine yield to that of their own preferred mCC. This finding was consistent with other results as subjective effects and product evaluation showed THS 2.2 Menthol was satisfactory to users, relieved urge-to-smoke and withdrawal symptoms comparably to mCC, and was therefore a suitable replacement for mCC shortly after the first days of use.

Initial changes in some CREs, which are relevant to disease pathways of smoking-related diseases, towards the direction of smoking abstinence suggest that the exposure reduction achieved with switching to THS 2.2 Menthol may translate into reduced risk of smoking-related diseases. However, a longer study period with an increased sample size is required to better determine these outcomes.

There were no SAEs reported by any randomized subject in this study and no randomized subjects were discontinued due to an AE. The majority of AEs were mild in severity; although 12 severe AEs were reported during the Ambulatory Period, all of which were due to abnormal clinical laboratory findings and were unrelated to IP use. The incidence of subjects experiencing AEs during the study was comparable between study arms; however, the frequency of AEs was higher in the THS 2.2 Menthol arm than the mCC and SA arms. As expected, the number of AEs and the percentage of subjects reporting AEs were higher in the Ambulatory Period.

Overall, the study results demonstrated sustained exposure reduction to HPHCs after switching to THS 2.2 Menthol, including in an ambulatory setting; and led to favorable changes in some CREs, while providing an acceptable alternative to users with regards to subjective experience; therefore, THS 2.2 Menthol might be a suitable substitute to mCC for adult smokers, with the potential to reduce the risk of developing smoking-related diseases over time.

**Final Report Date:** Version 1.0 / 25 May 2016

**Prepared in:** Microsoft word 2010



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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 <sub>2α</sub>	8-epi-prostaglandin F <sub>2α</sub>
11-DTX-B2	11-dehydro-thromboxane B2
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic and Chemical
AUC <sub>0-24 h</sub>	Area under the curve from 0 to 24 h
B	Blood sample required
B[a]P	3-hydroxybenzo(a)pyrene
BLOQ	below the limit of quantification
BMI	Body mass index
BoExp	Biomarker of exposure
CAF	Caffeine
C <sub>avg</sub>	Weighted average concentration over 24 hours
CC	Conventional cigarette
CEMA	2-cyanoethylmercapturic acid



CFR	Code of Federal Regulations
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COV	Close Out Visit
C <sub>peak</sub>	Peak plasma concentration
CRA	Clinical Research Associate
CRE	Risk marker, Clinical risk marker
CRF	Case report form
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical Study Report
CTCAE	Criteria for Adverse Events and Common Toxicity Criteria
CV	Coefficient of variation
CYP	Cytochrome P450
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
DLCO	Diffusion capacity for lung carbon monoxide
DMP	Data Management Plan
ECG	Electrocardiogram
EOS	End of the study
ePRO	Electronic Patient Reported Outcomes
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV <sub>1</sub>	Forced expiratory volume in 1 second
FRV	Forced residual volume
FTND	Fagerström Test for Nicotine Dependence



FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HEMA	2-hydroxyethylmercapturic acid
HIV	Human immunodeficiency virus
HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
HPHC	Harmful and potentially harmful constituents
hs-CRP	Highly sensitive C-reactive protein
HST	Human smoking topography
IB	Investigators Brochure
IC	Inspiratory capacity
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
(b) (4)	(b) (4)
KCO	Rate constant of carbon monoxide
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower than the limit of quantification
LS	Least squares
mCC	Menthol conventional cigarettes
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities



MEF 25-75	Mid expiratory flow
MHBMA	Monohydroxybutenyl mercapturic acid
MNWS-R	Minnesota Nicotine Withdrawal Scale
MNWS-R	Minnesota Nicotine Withdrawal Scale (revised)
MRTP	Modified risk tobacco product
NCS	Not clinically significant
NEQ	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)--butanone
NNN	N-nitrosonornicotine
NP	No preference
NRT	Nicotine replacement therapy
NSAIDs	Nonsteroidal anti-inflammatory drugs
o-tol	o-toluidine
PAH	Polycyclic aromatic hydrocarbons
PK	Pharmacokinetic
PMI	Philip Morris International
PP	Per protocol
PT	Preferred term
PX	Paraxanthine
QC	Quality Control
QSU-brief	Questionnaire of Smoking Urges-brief
RNA	Ribonucleic acid
SA	Smoking abstinence
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software





S-BMA	S-benzylmercapturic acid
SD	Standard deviation
SES	Socio-economic status
sICAM-1	Soluble inter-cellular adhesion molecule-1
SIV	Site Initiation Visit
SOC	System organ class
SOP	Standard Operating Procedure
S-PMA	S-phenylmercapturic acid
SQ	Smoking questionnaire
SSF	Study Site File
T <sub>0</sub>	Start time of the first product use
TC	Total cholesterol
TG	Triglycerides
THS	Tobacco Heating System
THS 2.2	Tobacco Heating System 2.2
THS m2.2	Tobacco Heating System 2.2 Menthol
TLC	Total lung capacity
t <sub>peak</sub>	Time to peak concentration
U	Urine sample required
ULOQ	Upper limit of quantification
US	United States
VA	Alveolar volume
VAS	Visual analogue scale
VC	Vital capacity
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 start on Day 30, Day 60, and Day 90, respectively, at the time of check-in of the subject on site prior to 08:30 AM until check-out of the day after on Day 31, Day 61, and Day 91, respectively.
End of study	End of Study was defined as the time of Discharge on Day 91 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 time of Discharge on Day 6.
Exposure Period in ambulatory setting	From the time of Discharge on Day 6 until the time of Discharge on Day 90 Visit (Day 91).
Menthol conventional cigarette (mCC)	The term 'menthol conventional cigarette' referred to manufactured and commercially available menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
mCC incompatible with HST SODIM <sup>®</sup> device	All mCCs that were incompatible with the HST SODIM <sup>®</sup> device (e.g., slim mCC).



Product use time periods	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 Period 4 Day 60 Visit to 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 to be informed of their randomization group prior to Day 1.
Run-in Period	Admission to site on Day -2 until 06:29 AM of Day -1.
Safety Follow-up	After the time of Discharge on Day 90 Visit (Day 91), a 28-day Safety Follow-up was done for the recording of spontaneously reported new adverse events (AEs)/serious adverse events (SAEs) and the active follow-up of ongoing AEs/SAEs by the site. In general, any AE was followed-up until resolved, 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 the time of informed consent form signature to the time of enrollment were considered a screening failure.
THS Menthol Tobacco Stick	The Tobacco Heating System (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 Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single THS Menthol Tobacco Stick).
Time of Discharge	Time of Discharge on Day 6: time when the subject was released from the site (Confinement Period) after all the procedures of the Day of Discharge (Day 6) had been conducted prior to entering into the Ambulatory Period. Time of Discharge on Day 90 Visit (Day 91): time when the subject was released from the site 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.



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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.
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## 5 ETHICS

### 5.1 Institutional Review Board

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF], subject information sheet, 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 and any other documents requested by an 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 local requirements, as applicable.

In accordance with GCP and 21 Code of Federal Regulations (CFR) part 56 (IRB review and approval of clinical investigation), 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 had been 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 1.0 on 02 July 2013. Approval was subsequently granted for Version 2.0 on 26 November 2013. Amendment 1 was incorporated into Version 2.0 of the protocol to include additional blood sampling for carboxyhemoglobin (COHb), as well as additional clarifications to the protocol; Version 3.0 was approved on 13 December 2013. Approval was subsequently granted for Version 4.0 on 14 January 2014. Amendment 2 was incorporated into Version 4.0 of the protocol to correct inconsistencies and typographical errors; Version 5.0 was approved on 14 April 2014.

The written approvals from the IRB were filed in the Principal Investigator file, and copies were filed in the Study Master File. The study started after the Sponsor had obtained written confirmation of favorable opinion/approval from the concerned IRB (Version 2.0).

A copy of the final protocol (Version 1.0 dated 26 June 2013), and the amended protocols (Version 2.0 dated 19 November 2013, Version 3.0, dated 11 December 2013, Version 4.0, dated 14 January 2014, and Version 5.0, dated 14 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 (1) and were consistent with ICH/GCP applicable regulatory principles.

The Principal Investigator agreed to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IRB. The Principal Investigator and the Sponsor signed the protocol (and protocol amendments) to confirm this agreement. A copy of the Declaration of Helsinki (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 had 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 which included both the subject information sheet and informed consent by the date, time and signature of both the subject and the person who conducted the informed consent discussion during the Screening Visit. No study-specific procedures were performed before the ICF had been signed.

The original, dated and signed ICF 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. Any additional analysis performed was to be covered by data confidentiality, as for the main analysis described in this protocol.

## 5.4 Sample Banking Informed Consent Form

In addition to the ICF for the participation in the study, subjects were provided with information and were asked for consent to collect samples for additional bio-banking.

One separate ICF was to obtain consent for serum, plasma, and urine collection and long-term storage for biomarkers of exposure (BoExp) and risk markers (CREs). No genetic or transcriptomics testing was to be performed on these samples. A copy of the Subject Information and ICF for optional long-term storage (bio-banking) of urine, plasma, and serum samples is provided in [Appendix 16.1.3](#).



An additional, separate ICF was to obtain consent for collection and long-term storage of blood for further transcriptomics (pharmacogenomics) analysis in order to study the variation of the ribonucleic acid (RNA - messenger RNA [mRNA] and micro RNA [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). 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 mCC showed that using THS 2.1, the earlier version of THS 2.2, resulted in significant variation of RNA characteristics as compared to smoking conventional cigarettes (CC). A copy of the Subject Information and ICF for genetic and pharmacogenomic analysis is provided in [Appendix 16.1.3](#).

The same ICF was used to obtain consent for collection and long-term storage of samples from nasal epithelial and buccal collections in order to provide biological material for molecular profiling. The changing molecular profiles were to provide insight into the biological processes that took place in mCC, THS 2.2 Menthol, and SA arms. It was anticipated that, given the similarities in the cell types along the respiratory tract, the biological processes identified in the nasal and buccal tissues might reflect those that give rise to lung diseases that are etiologically linked to smoking (2).

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 answered 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, time, and signature of both the subject and the Principal Investigator and personnel who conducted the informed consent discussion.

The subject's consent to collection and 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 their providing consent for sample bio-banking.



## 6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

<b>Study Sites</b> (Clinical Conduct)	Covance Dallas Site 1341 W. Mockingbird Ln., Suite 400E Dallas, TX 75247  Covance Daytona Beach Site 1900 Mason Ave., Suite 140 Daytona Beach, FL 32117
<b>Principal Investigators</b>	Dr William Lewis (Covance Dallas) Dr Frank Farmer (Covance Daytona Beach)
<b>Sponsor</b>	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	Ruben Rosoky, MD PhD MFPM (as of 18 November 2015) Alexandr Meszros, MD (as of 27 March 2015 until 18 November 2015) Kausar Aamir, MD, PhD (from 08 December 2014 until 27 March 2015) Tamara Koval, MD (until 08 December 2014)
Biostatistician	Guillaume de La Bourdonnaye, MEng, MSc
Clinical Study Manager	Dimitra Skiada
Study Data Manager	Sarah Merlet
<b>Clinical Laboratory and Analytical Sites</b>	
Clinical Safety Laboratory (Screening and for randomized subject visits)	(b)(4)
Project manager	(b)(4)
Risk markers (Apo A1, Apo B, Fibrinogen, HbA1c, Homocysteine, HDL-C, LDL-C, sICAM1, and hs-CRP)	Covance Central Laboratory Services, Inc 8211 SciCor Drive Indianapolis, IN46214 - 2985
Technical Writer, Global Laboratory Support Services	Carmen Y Alsum BSc





Plasma and Urine BoExp <sup>1</sup> (Urine: 3-HPMA, Total NNN, CEMA, HEMA, B[a]P, HMPMA, Total NNAL, and NEQ, 8-epi-PGF <sub>2α</sub> , 11-DTX-B2, 4-ABP, 1-NA, 2-NA, and o-tol; Plasma: nicotine and cotinine, caffeine and paraxanthine, cotinine and trans-3'-hydroxycotinine) COHb <sup>1</sup> in whole blood <sup>1</sup> See Table 1 for definitions of BoExp	Celerion Inc. 621 Rose Street, Lincoln Nebraska 68502
Bioanalytical Principal Investigator Quality Assurance Manager	Kirk Newland, BSc Crystal Bickford, BA
Urine S-BMA, S-PMA, MHBMA, and Total 1-OHP <sup>1</sup> <sup>1</sup> See Table 1 for definitions of BoExp	Celerion Switzerland AG Allmendstrasse 32 CH-8320 Feraltorf (Zürich) Switzerland
Bioanalytical Principal Investigator Quality Assurance Manager	Markus Bachmann, PhD Diana Burgin
Exploratory Markers: Urine Ames mutagenicity	Labstat International ULC 262 Manitou Drive, Kitchener ON, Canada N2C 1L3
Contributing Scientist	Amit Trivedi, PhD
Oxysterols	Philip Morris Products S.A. PMI Research and Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Manager Metabolomics & Analyt.Chemistry	Mark Bentley
<b>Bio-Banking Samples</b>	(b)(4)
Project Manager	(b)(4)
<b>Topography</b>	Philip Morris International. Research and Development, Human Smoking Topography Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Human Smoking Topography Scientists	Anthony Bruchet Valerie Poux
<b>Clinical Research Organization (Study Monitoring)</b>	Covance Early Clinical Development Services 3402 Kinsman Boulevard. Madison, WI 53704
Project Manager Clinical Research Associate	Jasmine Ropers Ann Hintz (until 20 June 2014) Mary Martinez (from 20 June 2014 until 05



	November 2014)
	Esther Clements (as of 05 November 2014)
<b>Randomization Interactive Web and Voice Response System</b>	(b)(4)
Project Manager	(b)(4)
<b>Electronic Patient Reported Outcome (EPRO)</b>	(b)(4)
Senior Project Manager	(b)(4)
<b>Clinical Research Organization (Serious Adverse Event and Pregnancy Reporting)</b>	United BioSource Corporation Safety 16, Chemin des Coquelicots 1214 Vernier/Geneva Switzerland
Safety Scientist	Alexandra Banderier
<b>Clinical Research Organization (Data Management and Study Reporting)</b>	
Project Manager	Jo Taylor, BSc, PhD Maidenhead, UK
Medical Monitor	Katerina Bovtenko, MD, MSc Maidenhead, UK
Data Manager	Mary Russo Princeton, NJ USA
Pharmacokineticist	Stuart Hossack, BSc Leeds, UK
Statistician	John Hunter, BSc, MSc Madison, WI USA (as of 12 January 2015) Andrew Hedge, BSc, MSc Leeds, UK
Medical Writer	Louise Wakenshaw, BSc, PhD (as of 08 January 2016) Andrew Senior, BSc, PhD Leeds, UK

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

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



## 7 INTRODUCTION

Cigarette smoking causes pulmonary, cardiovascular, and other serious diseases in smokers (3). There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers cannot refrain from smoking or decide to continue smoking. 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 United States Food and Drug Administration (FDA) as modified risk tobacco products (MRTPs) (4).

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, and to be assessed in this study, is the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for 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 to maintain approximately a 6-minute session. Unlike CC, THS Menthol Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of earlier development of THS 2.2 Menthol are described in the IB (5), 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. Further details are provided in the IB (5).

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 aerosol fractions, total particulate matter, and gas vapor phase 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.

The previous version of the THS 2.2 non-Menthol, namely the THS 2.1, was tested in 2 exploratory clinical studies to measure the nicotine plasma kinetic profile ([www.clinicaltrial.gov](http://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](http://www.clinicaltrial.gov) identifier: NCT01780714). The observed nicotine plasma pharmacokinetic (PK) profile for THS 2.1 was similar to CC as well, with substantial reductions in the exposure to the majority of selected HPHCs (5). Clinical studies conducted so far have revealed no safety concern for either 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 who continued to smoke their preferred brand of mCC in a confinement setting for 5 days followed by an ambulatory setting of 86 days. Smokers who were asked to abstain from smoking were used as a reference point. The smokers in 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., cytochrome P450 1A2 [CYP1A2] and cytochrome P450 2A6 [CYP2A6] enzymatic activity, PK profile of nicotine and cotinine, product evaluation, product use and subjective effects related to smoking, 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 (Table 1) to HPHCs (except Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [Total 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) (concentration adjusted for creatinine) in 24-hour urine, and COHb in blood (expressed as % of 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.

### 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 smoking abstinence (SA).

#### Endpoints

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

Endpoints

- 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 on 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 (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 5, and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
5. To describe the 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 (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
  - Weighted average concentration over 24 hours on Day 5.
6. To describe the change in CYP1A2 enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoints

- Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5 and Day 90 Visit.
7. To determine the changes in lung functions in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints

- Full lung functions: diffusion capacity for lung CO (DLCO), rate constant of CO (KCO), forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC), vital capacity (VC) expressed as L, total lung capacity (TLC), forced residual volume (FRV), inspiratory capacity (IC), mid expiratory flow (MEF 25-75).
8. 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.
  - Electrocardiogram (ECG).
  - Clinical chemistry, hematology, and urinalysis safety panel.
  - Physical examination.
  - Concomitant medications.
9. 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/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- Highly 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.
- Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) in serum on Day 90 Visit.
- Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6/Discharge Confinement, on Day 30 Visit, Day 60 Visit, and Day 90 Visit.



- White blood cell (WBC; leukocytes) and platelet count in blood on Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
- 8-epi-prostaglandin F<sub>2α</sub> (8-epi-PGF<sub>2α</sub>) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5 and on 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)-1-butanone (NNK)	Urine
Secondary BoExp	carbon monoxide	CO	Exhaled breath
	Total 1-hydroxypyrene (Total 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-toluidine	Urine
	2-cyanoethylmercapturic acid (CEMA)	acrylonitrile	Urine
	2-hydroxyethylmercapturic acid (HEMA)	ethylene oxide	Urine
	3-hydroxybenzo(a)pyrene (B[a]P)	benzo(a)pyrene	Urine
	3-hydroxy-1-methylpropyl-mercapturic acid (HMPMA)	crotonaldehyde	Urine
	S-benzylmercapturic acid (S-BMA)	toluene	Urine
BoExp to Nicotine	nicotine equivalents (NEQ)		
	free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free <i>trans</i> -3'-hydroxycotinine, <i>trans</i> -3'-hydroxycotinine-glucuronide	nicotine	Urine
	nicotine	nicotine	Plasma
	cotinine	nicotine	Plasma





### 8.3 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 (QSU-brief); Minnesota Nicotine Withdrawal Scale (MNWS) – Revised (MNWS-R) on Day 5 and Day 90 Visit; and nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire score on Day 90 Visit.
- CYP2A6 activity: in plasma on Day 6/Discharge Confinement, and on Day 90 Visit using the molar metabolic ratio of *trans*-3'-hydroxycotinine/cotinine.

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

#### Endpoints

- Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
- Smoking puffing behavior: HST parameters and HST questionnaire.
- The following parameters measured per cigarette from the HST device.
  - Total number of puffs.
  - Total puff volume.
  - Average puff volume.
  - Average puff duration.
  - Total puff duration.
  - Average flow.
  - Peak flow.
  - Total inter puff interval.
  - Average inter puff interval.
  - Total smoking duration.
  - Total work.
  - Average work.
  - Average pressure drop.
  - Average peak pressure drop.
  - Smoking intensity.
  - Puffing time index.
  - Puff frequency.

3. To describe the following parameter 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.



4. To describe the changes in levels of oxysterols on Day 6/Discharge Confinement and Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol, and in smokers switching from mCC to SA.

#### Endpoints

- Plasma concentrations of:
  - 6 $\alpha$ -hydroxy-5 $\alpha$ -cholestane.
  - 7 $\alpha$ -hydroxycholesterol.
  - 5 $\alpha$ ,6 $\alpha$ -epoxycholestanol.
  - 7-ketocholesterol.
  - 7 $\beta$ -hydroxycholesterol.
  - 5 $\beta$ ,6 $\beta$ -epoxycholestanol.
  - 24(R)-hydroxycholesterol.
  - 25-hydroxycholesterol.
  - 27-hydroxycholesterol.
  - Total cholesterol (TC).
  - 22(R)-hydroxycholesterol.
  - 4 $\beta$ -hydroxycholesterol.
- 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 usage log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary by product preference.
- 6. To describe the smokers' mental state for the intention to quit at Screening, on Day -2, Day 30 Visit, Day 60 Visit, and Day 90 Visit.

#### Endpoint

- By the means of the Prochaska 'Stage of Change' questionnaire.
- 7. To describe the changes and reductions in the levels of urinary BoExp and CREs measured in 4-hour urine fraction on Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

#### Endpoints

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



- Urinary CREs (expressed as quantity excreted and concentration adjusted for creatinine) in 4-hour urine fraction:
  - 8-epi-PGF<sub>2α</sub>.
  - 11-DTX-B2.
- 8. To evaluate in smokers switching from mCC to THS 2.2 Menthol, and smokers continuing smoking mCC the relationship between\* :

Endpoints

- Primary and secondary BoExp and NEQ on Day 5 in 24-hour urine and on Day 90 Visit.

\*The reporting of the objective was the subject of a separate report.

- 9. To determine the concordance between the results for BoExp and CREs in 24-hour urine and in 4-hour urine fraction\* .

Endpoints

- MHBMA, 3-HPMA, S-PMA, Total NNAL, Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, and NEQ (expressed as quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at baseline and on Day 90 Visit.
- 8-epi-PGF<sub>2α</sub> and 11-DTX-B2 (expressed as quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at baseline and on Day 90 Visit.
- MHBMA, 3-HPMA, S-PMA, Total NNAL, Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, and NEQ (expressed as change in quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and change in concentration adjusted for creatinine in 4-hour urine fraction from baseline to Day 90 Visit).
- 8-epi-PGF<sub>2α</sub> and 11-DTX-B2 (expressed as change in quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and change in concentration adjusted for creatinine in 4-hour urine fraction from baseline to Day 90 Visit).

\*The reporting of the objective was the subject of an appendix to the main Clinical Study Report (CSR).

- 10. To monitor the BoExp in subjects quitting smoking according to the time since they quit\*.

Endpoints

- Carbon monoxide (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 collection and 4-hour urine fraction.



- NEQ (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine collection and 4-hour urine collection.
  - Selected CREs (hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, HbA1c, Apo A1, Apo B, sICAM-1, WBC (leukocyte) count, platelet count, 8-epi-PGF<sub>2α</sub>, 11-DTX-B2) in respective body matrix when available.
- \*The reporting of the objective was the subject of an appendix to the main CSR.

## 8.4 Study Hypotheses and Evaluation Criteria

### 8.4.1 Hypotheses

The hypothesis tested was that the geometric mean levels 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 on Day 5 then the endpoint was further tested Day 90.

### 8.4.2 Evaluation Criteria

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 at the Day 90 Visit 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.





## 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 average daily mCC 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). A demonstration of the THS 2.2 Menthol 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

The Run-in Period was defined as from Admission on Day -2 until 06:29 AM on 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 only performed after 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 who participated 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 06:30 AM on Day -1 until 06:29 AM on Day 1. All subjects continued smoking their preferred brand of mCC, and baseline values were recorded. On Day -1 and Day 0, smoking was allowed from 06:30 AM onwards until around 11:00 PM. However, on Day 0, smoking was allowed only after sampling for CYP2A6, MNWS-R and cough questionnaires, and full lung functions had been conducted.



A 4-hour urine fraction was collected on Day -1. On Day 0, 24-hour urine was collected starting in the morning and ending 24 hours later on Day 1, prior to the randomized Exposure Period.

On Day 0, subjects were randomized to 1 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 site staff on Day 1 prior to 06:30 AM.

#### Exposure Period

The Exposure Period was defined as from 06:30 AM on Day 1 until time of Discharge on Day 90 Visit (Day 91), and included both the Exposure Period in Confinement and the Exposure Period in the Ambulatory Period.

#### 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 Confinement was defined as from 06:30 AM on Day 1 until time of Discharge on Day 6 consisting of 5 days of *ad libitum* use of the assigned product from 06:30 AM onwards until around 11:00 PM in THS 2.2 Menthol and mCC arms. 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. Use of any tobacco/nicotine-containing product other than the assigned product/regimen was not allowed and may have, at the discretion of the Principal Investigator, resulted in subject discontinuation.

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

On Day 6/Discharge Confinement, the safety procedures were conducted before Discharge of the subject from the clinic after 9 days in a confined setting. Use of products



was allowed on Day 6/Discharge Confinement in the THS 2.2 Menthol and mCC arms according to product arm allocation, but only after the sample for CYP2A6 activity, MNWS-R and cough questionnaires, and full lung function had been performed.

#### Exposure Period in Ambulatory Setting

The Exposure Period in the ambulatory setting was defined as from time of Discharge on Day 6 until time of Discharge from the Day 90 Visit (Day 91).

At the end of the Confinement Period prior to Discharge on Day 6, subjects were instructed to continue their assigned product/regimen in an ambulatory setting for 86 days. All subjects in the SA arm received smoking cessation counseling and were able to use nicotine replacement therapy (NRT) if considered necessary by the Principal Investigator or requested by the subject.

Subjects were required to make 3 visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each Ambulatory Visit covered 2 consecutive days on site. For the Day 30 Visit and Day 60 Visit, the subject checked in in the morning prior to 08:30 AM, and checked out the next day. For the Day 90 Visit, the subjects checked in in the morning prior to 08:30 AM, and were discharged on Day 91 after all of 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 was followed by the collection of a 4-hour urine fraction.

During the Ambulatory study visits, subjects in the THS 2.2 Menthol and mCC arms were allowed to use their assigned product from the time of check-in, prior to 08:30 AM, until around 11:00 PM. On Day 31 and Day 61, product use was allowed from 06:30 AM. On Day 91, product use was allowed only after the sample for CYP2A6 activity and full lung function had been performed until Discharge on Day 91.

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

On Day 91, 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/site staff.



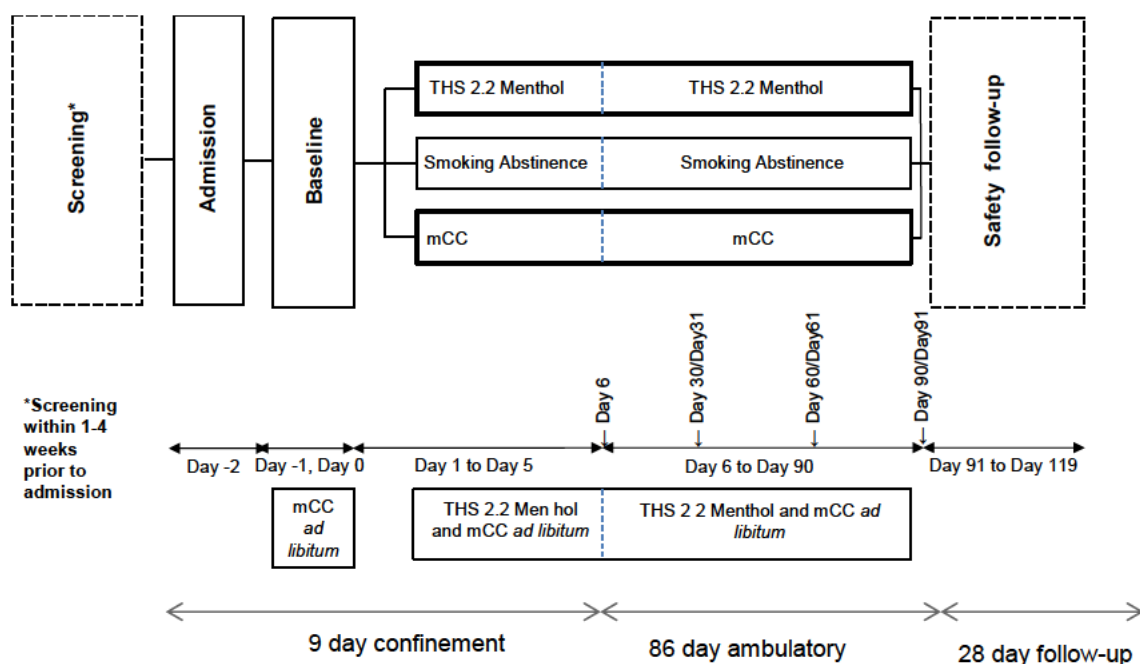
### Safety Follow-up Period

After discharge from the Day 90 Visit (Day 91), subjects entered a 28-day Safety Follow-up Period during which there was recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs were 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 (EOS) was defined as the end of the 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 on a daily basis.

Any subject who wanted to quit smoking during the study (taking into account the outcome from the Prochaska 'Stage of Change' questionnaire), was encouraged to do so, and referred to appropriate medical services. This would not have affected the subject's financial compensation and the subject was to remain in the study.

**Figure 1 Study Flow Chart**



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

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 to be assessed in this study was derived from the World Health Organization (WHO) (6) and the draft guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke (7).

In the WHO list, 9 HPHCs (acrolein, CO, 1,3-butadiene, benzene, NNN, NNK, acetaldehyde, B[a]P, and formaldehyde) with evidence of carcinogenicity, respiratory and cardiac toxicity were recommended to be measured as priority in the smoke chemistry for mandated lowering (6). In addition to the 9 HPHCs recommended to be measured by the WHO list, an additional 9 HPHCs were added (18 HPHCs in total in cigarette smoke) for reporting from the FDA list (7).

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

- HPHCs are several-fold higher in smokers than in smokers abstinent from smoking (8).
- 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 phases of the THS 2.2 aerosol.
- They exhibit, on average, an elimination half-life of  $\leq 24$  hours. Therefore, the 5 days of exposure was deemed sufficient to reach the steady state with the THS 2.2 Menthol and SA arms (4 to 5 times the half-life will lead to less than 5% of the original exposure levels of assessed biomarkers on Day 5).
- They include a broad variety of chemical classes and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential).
- They were decreased in smokers who switched to another tested candidate MRTP for 5 days, similarly to that observed in smokers who stopped smoking (data on file from a previous study (9)).

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. 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 the primary endpoint after 90 days of THS 2.2 Menthol use as:

- This biomarker is tobacco-specific (10), and exhibits, on average, an elimination half-life of 10 to 15 days. Therefore, the 91 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 (9)).

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 (7). 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 (6).

In addition, some CREs were selected in order to evaluate subjects' biological changes in THS 2.2 Menthol arm as compared to 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:

- CYP1A2 activity, the enzyme which mainly metabolizes caffeine, is decreased as from 5 days of SA (11) and after 5 days of use of another candidate MRTP (9) and data on file from a previous study.
- Platelet function was assessed by measuring 11-DTX-B2 (a major stable metabolite of thromboxane A2, which elicits mainly platelet aggregation). This marker was decreased after 1 week of SA (12) and after 5 days of use of another candidate MRTP (9).
- Blood pressure, hs-CRP, fibrinogen, homocysteine, fasting blood glucose, LDL, HDL, TG, TC, HbA1c, waist circumference, sICAM-1, WBC (leukocytes), Apo A1, Apo B, and 8-epi-PGF<sub>2α</sub> were evaluated as additional CREs (13, 14) for cardiovascular monitoring purposes. According to the literature, some of these CREs are known to be sensitive to smoking cessation: the levels of high density lipoprotein cholesterol (HDL-C) increase whereas the levels of sICAM-1, WBC (leukocytes), and 8-epi-PGF<sub>2α</sub> decrease following 1 to 3 months of smoking cessation (8, 13).
- 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 (12).



- Oxysterol was measured in the study to verify that the reduction observed in animal models of disease upon smoking cessation and switching to candidate MRTP (in-house data) was also observed in humans.
- CYP2A6 activity, the enzyme involved in nicotine metabolism was assessed in this study to evaluate if the use of THS 2.2 Menthol impacted the activity of this enzyme.
- Lung function including DLCO, FEV<sub>1</sub>, FVC, VC, TLC, FRV, IC, and MEF 25-75 were assessed in this study as it has been shown that some of these parameters may be improved early on after smoking cessation, and are markers correlating with early but still reversible changes occurring in the distal airway upon smoking (14, 15).

Twenty-four-hour urine was collected in this study as it is a well-established method to measure the levels of excretion of BoExp. Four-hour urine fractions were also collected to better understand their accordance with 24-hour urine in the perspective of using such fractions in future ambulatory studies thereby minimizing operational and subject constraints.

The minimum age of 22 years in the inclusion criteria was selected based on:

- The legal age of smoking in the location of the chosen sites was 19 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 stopped 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. 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.

The Confinement Period provided information on maximum possible exposure reductions in a well-controlled environment and allowed full control of daily cigarette consumption. 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 is 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 in order to minimize any changes in their smoking behavior.

### 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 at a minimum 22 years of age.
3. Smoking, apparently 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, vital signs, physical examination, ECG, chest X-ray, and medical history).
4. Subject smoked at least 10 commercially available mCCs per day (no brand restrictions), 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  $\geq 200$  ng/mL).
5. The subject did not plan to quit smoking within the next 6 months as assessed by the Prochaska 'Stage of Change' questionnaire.
6. The subject was ready to comply with study protocol (e.g., readiness to accept interruptions of smoking for up to 91 days and to use THS 2.2 Menthol\*).

\* readiness to use THS 2.2 Menthol was asked on Day of Admission after the product test.

#### 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, subject in a social or sanitary establishment, prisoners, or subjects who are involuntarily incarcerated).
3. The subject had clinically relevant diseases which required medications (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition; including safety laboratory as per Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] Version 4.03), which in the opinion of the Principal Investigator would have jeopardized the safety of the subject.





4. Subject who had  $FEV_1/FVC < 0.7$  and  $FEV_1 < 80\%$  predicted value at post-bronchodilator spirometry (16).
5. Subject with asthma condition ( $FEV_1/FVC < 0.75$  and reversibility in  $FEV_1 > 12\%$  [or  $> 200$  mL] from pre- to post-bronchodilator values).
6. Subjects with renal insufficiency as defined by serum creatinine levels of  $> 1.3$  mg/dL for females and  $> 1.5$  mg/dL for males.
7. The subject had a body mass index (BMI)  $< 18.5$  or  $\geq 35$  kg/m<sup>2</sup>.
8. As per Principal Investigator judgment, the subject had medical conditions which required, or would require 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.
9. Any subject with a history of AEs linked to caffeine or caffeine-containing drugs (e.g., Vivarin), such as but not limited to hypersensitivity or allergy.
10. 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.
11. The subject had received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug (whichever is longer) prior to the Admission Day (Day -2), which had an impact on CYP1A2 or CYP2A6 activity.
12. 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 to be decided at the discretion of the Principal Investigator if these could potentially interfere with the study objectives or subject's safety.
13. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid.
14. The subject had a positive alcohol test and/or the subject had a history of alcohol abuse that could interfere with the subject's participation in the study.
15. The subject had a positive urine drug test.
16. Positive serology test for human immunodeficiency virus (HIV)1/2, hepatitis B, or hepatitis C.
17. Donation or receipt of whole blood or blood products within 3 months prior to Admission.
18. The subject was a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
19. 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, and child).
20. The subject had participated in a clinical study within 3 months prior to the Screening Visit.

Additionally, women were excluded if:

21. Subject was pregnant (did not have negative pregnancy tests at Screening and at Admission) or was breast feeding.
22. 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 are not effective methods) from Screening until the end of the safety Follow-up Period. Hysterectomy, tubal ligation, bilateral oophorectomy, or post-menopausal status were reasons for not needing to use birth control. Post-menopausal status was defined as women who had not experienced menses for greater than 12 months. If a woman claimed she was post-menopausal, but had had her menses within 12 months, a follicle-stimulating hormone test was to be performed and must have been within acceptable limits.

### 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 withdrew or was removed from the study (both Confinement and Ambulatory Periods), the whole safety examination procedure planned at the Day of Discharge on Day 6 was performed as soon as possible after the time of withdrawal unless the subject had withdrawn their informed consent to do so. After the time of withdrawal, the subject entered into the 28-day period of Safety Follow-up. Subjects withdrawn or removed from the study could not re-enter the study.

Subjects were to be 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) which at the discretion of the Principal Investigator no longer justified the subject's participation in this study.
- Positive pregnancy testing (any invasive procedures, including the drawing of blood were not to be performed after diagnosis of pregnancy).
- The Sponsor or Principal Investigator terminated the study. If the Sponsor or the Principal Investigator decided to prematurely terminate the study, the subject was promptly informed and followed the safety procedures for early termination. The head of the medical institution reported the fact and the reason in writing to the IRB.
- Withdrawal was considered to be in the best interest of the subject or the other subjects.

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

- Lost to follow-up.
- Concomitant treatment with non-authorized medication as defined in the context of this study (in general, any concomitant medication was to be discussed with the Contract Research Organization [CRO] Medical Monitor on an ongoing basis).



- During the Confinement Period, if a subject used any mCC or nicotine-/tobacco-containing product other than the product/regimen he/she was assigned to, he/she was to be discontinued from the study.
- Non-compliance to the study procedures based on the judgment of the Principal Investigator.

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 withdrawn or 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 who did not meet the entry criteria at Admission Day (Day -2), were considered screening failures 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 to be immediately discontinued from the study when the violation was detected. If subjects were not yet randomized, they could be 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.

## 9.4 Investigational Products

### 9.4.1 Investigational and Reference Cigarettes

The THS 2.2 Menthol 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:





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 main power source.
THS 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 design was to provide an acceptable experience in which the HPHC level in the aerosol was substantially reduced in comparison with mCC.

Pack batch number of packed THS Menthol Tobacco Sticks: B-08545. Production date: 28 October 2013; Expiry dates: 27 July 2014 and 27 November 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 mCCs were not provided by the Sponsor and subjects were not allowed to roll their own mCCs.

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 staff. In case more mCC were needed during the Confinement Period, re-supply of mCC could be envisaged.

During the Ambulatory Period, subjects purchased their own preferred brand of mCC.





### 9.4.3 Packaging and Labeling

At Admission, all study subjects provided the anticipated amount of mCC for use in the Confinement Period in sealed packs to the study site staff. The mCC packs provided by the subjects were not to be opened and the cellophane wrapper was to be intact.

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

### 9.4.4 Storage and Accountability

A person in the site staff designated by the Principal Investigator was responsible for the storage and accountability of the investigational products (IPs), in accordance with the Sponsor's requirements.

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

#### 9.4.4.1 Confinement Period

On each day of the Confinement Period, study site staff recorded on the accountability log every occasion from Day -2 to time of Discharge on Day 6 that mCCs were dispensed to a subject by the study site staff and every occasion from Day 1 to time of Discharge on Day 6 that the THS 2.2 Menthol product components (i.e., THS Tobacco Stick Holder, THS Charger, THS accessories) and THS Menthol Tobacco Sticks were dispensed to a subject.

Subjects returned each butt of mCC immediately after use from Day -2 to Day 6/Discharge Confinement 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 were collected from Day 1 to Day 5, using dedicated vials for accountability and subsequent analysis of potential combustion occurrences. This was also documented in appropriate log.



#### 9.4.4.2 Ambulatory Period

Subjects in the THS 2.2 Menthol arm were to return any unused packs, empty packs, and partially used packs of THS Menthol Tobacco Sticks and the THS 2.2 Menthol product components that they had used to the site for accountability.

All tobacco plugs from THS Menthol Tobacco Sticks used after check-in at the investigational site until around 11:00 PM on Day 30 Visit, Day 60 Visit, and Day 90 Visit were collected in dedicated vials for subsequent analysis of potential combustion occurrences.

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 the time of Discharge from the clinic, the site staff 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 had been met, randomization was done through the (b) (4) 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 to 19 mCC/day, female smokers who smoked 10 to 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 using their allocated product 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.

##### 9.4.7.1 Run-in Period

Smoking *ad libitum* was allowed prior to Admission and throughout the day except during the procedures at the discretion of the site. Smoking was allowed from the time of check-in of the subject until around 11:00 PM. All subjects (except women with a positive pregnancy test at Screening or at Admission) underwent a THS 2.2 Menthol product test.

Following the confirmation that the subject was able and willing to use the THS 2.2 product, subjects were enrolled.

##### 9.4.7.2 Baseline Period

During the Baseline Period, all subjects were allowed to continue smoking *ad libitum* their single preferred usual brand of mCC. On Day -1, smoking was allowed from 06:30 AM onwards until around 11:00 PM. However, on Day 0, smoking was allowed only after sampling for CYP2A6 activity, MNWS-R and cough questionnaires, and full lung functions had been conducted.

##### 9.4.7.3 Exposure Period

During the exposure Confinement Period from Day 1 until the time of Discharge on Day 6, subjects were not allowed to use any nicotine/tobacco-containing products other than their assigned product/regimen. Smoking was allowed from 06:30 AM onwards until around 11:00 PM. On Day 6/Discharge Confinement, the use of the products (THS 2.2 Menthol or mCC) was allowed only after the sampling for CYP2A6 activity, cough and MNWS-R questionnaires, and full lung functions had been done. Smoking was not allowed in the SA arm.

During the exposure Ambulatory Period, subjects were instructed to continue using exclusively their assigned product/regimen. Subjects in the SA arm were instructed to abstain from smoking. The use of any CCs (menthol or non-menthol) or nicotine/tobacco-containing products other than the product/regimen the subject was assigned to was documented in the daily product use electronic diary.



In the morning of the Day 91/Discharge Ambulatory, subjects in THS 2.2 Menthol and mCC arms were not allowed to use their assigned product until the sampling for CYP2A6 activity, and full lung functions had been conducted at the clinic. Smoking was not allowed in the SA arm.

During the study, any subject who wanted to quit smoking was encouraged to do so and referred for further treatment as per the standard of care in the country in which the study was conducted.

#### 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 the THS 2.2 Menthol from Day 1, 06:30 AM onwards until time of Discharge on Day 6. At time of Discharge on Day 6 and on each Ambulatory Visit, subjects were instructed to continue exclusively using the THS 2.2 Menthol *ad libitum* until time of Discharge of Day 90 Visit (Day 91).

#### 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 time of Discharge on Day 6. At the time of Discharge on Day 6, subjects were informed that they could continue to smoke their mCC *ad libitum* until the time of Discharge on Day 90 Visit (Day 91).

#### 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 the time of Discharge on Day 6. They were not provided with medication supportive for SA or NRT.

On Day 6/Discharge Confinement, on each Ambulatory Visit, and at any appropriate occasion, subjects in the SA arm were instructed to remain abstinent with or without NRT (no other medication supportive for SA was allowed) until time of Discharge on Day 90 Visit (Day 91).

#### 9.4.7.3.4 Safety Follow-up Period

During the safety Follow-up Period (after the time of Discharge on Day 90 Visit [Day 91] until Day 119), there were no smoking restrictions. 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.





#### 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

From Day -2 onwards during the Confinement Period, each mCC was individually dispensed to the subjects. Subjects in the THS 2.2 Menthol arm were provided by the site personnel with THS Menthol Tobacco Sticks from Day 1 to Day 6/Discharge Confinement, stick by stick. One mCC/THS Menthol Tobacco Stick was allowed at a time, as per the study design, and was 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 -2 for mCC and from Day 1 for THS Menthol Tobacco Sticks onwards. The start of product use on each day corresponded to the time of dispense of the first mCC/THS Menthol Tobacco Stick. The subject was not to take a puff of the THS Menthol Tobacco Stick during the pre-heating time. 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 the THS 2.2 Menthol including the 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 delivery of THS Menthol Tobacco Sticks in between 2 visits was arranged if requested. Subjects in the mCC arm bought their mCCs directly from shops and were not reimbursed.

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

#### 9.4.10 Blinding/Unblinding

This was an open-label study, with a limited degree of blinding up to the data review and in the decision of data analysis process. The subjects and Principal Investigators were unblinded to subject's arm. Members of the Sponsor and the CRO personnel were blinded to the randomized product, with blinded and unblinded personnel roles defined by the data review plan.

**Table 3 Blinding Scheme**

Blinded Study Personnel	End of Blinding Period
PMI and Covance study statisticians	After the database lock, whichever came last
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. (Could have been actively unblinded before that time point as appropriate, in case of the occurrence of any safety question)

Abbreviations: PMI = Philip Morris International.

As part of the PMI Quality Control (QC) activity, data listings were reviewed by Covance and PMI before database lock, with no access to the randomization arm information. Full details including the definition of the blinded and unblinded PMI study teams are available in the data review plan (Version 2.0 Date: 2 April 2015).

#### 9.4.11 Prior and Concomitant Therapy

No medications were to be taken during the study from the screening to the EOS (time of Discharge from Day 90 Visit [Day 91] plus 28-day safety Follow-up Period) 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 decision regarding the prescribing of medication was made in the best interests of the subject.

Concomitant medication was first assessed at the Screening Visit. To be eligible for the study, any medication with impact on 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 entire study until Day 91/Discharge Ambulatory (completion of the study).

During the Ambulatory Period, subjects in the SA arm were provided with NRT if considered necessary by the Principal Investigator or requested by the subject. No medication supportive of SA other than NRT was allowed.

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. Acetaminophen was allowed at a daily total dose of up to 3000 mg. Any medication (except medication containing estrogen) with an impact on CYP1A2 and/or 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 shown in [Table 4](#) and [Table 5](#) are a selection of drugs considered to have an impact on CYP1A2 and/or CYP2A6 activity ([17](#), [18](#)) ([8](#)). Prior to database close, concomitant medication was assessed according to their potential impact on CYP1A2 and CYP2A6 activity and potential impact on the study results.

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

<b>Inhibitor</b>	<b>Drug Class</b>
Amlodipine	Calcium channel blocker (dihydropyridine) + angiotensin-converting-enzyme inhibitor
Cimetidine	H2 blocker
Ciprofloxacin	Antibiotic
Fluvoxamine	Antidepressants
Fospropofol	Short acting hypnotic/sedative/anesthetic agent
Gemfibrozil	Lipid-regulating agent
Ketoconazole	Antifungal
Diclofenac	Nonsteroidal anti-inflammatory drug
Methoxsalen	8-methoxypsoralens
Mexiletine	Antiarrhythmic
Miconazole	Antifungal
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
<b>Inducer</b>	<b>Drug Class</b>
Carbamazepine	Anticonvulsant
Phenobarbital	Barbiturate
Primidone	Barbiturate/anticonvulsant
Rifampin	Antimycobacterial agent
<b>Substrate</b>	<b>Drug Class</b>
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	Anticancer agent
Duloxetine	Antidepressant
Estradiol	Hormonal agent
Estrogens, conjugated A/synthetic	Hormonal agent





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Estrogen, conjugated equine	Hormonal agent
Estrogen, esterified	Hormonal agent
Estropipate	Hormonal agent
Flutamide	Hormone/anti-androgene
Fluvoxamine	Antidepressant
Guanabenz	Alpha-2 adrenergic agonist
Mexiletine	Antiarrhythmic 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

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Data source: (19)

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

<b>Inhibitor</b>	<b>Drug Class</b>
Amiodarone	Antiarrhythmic agent, Class III
Desipramine	Antidepressant
Isoniazid	Anti-bacterial drug
Ketoconazole	Antifungal medication
Letrozole	Anti-estrogen drug
Methoxsalen	Systemic psoralens
Miconazole	Antifungal medication
Tranlycypromine	Antidepressant
<b>Inducer</b>	<b>Drug Class</b>
Amobarbital	Barbiturate
Pentobarbital	Barbiturate
Phenobarbital	Barbiturates/anticonvulsant
Rifampin	Antimycobacterial
Secobarbital	Barbiturate
<b>Substrate</b>	<b>Drug Class</b>
Dexmedetomidine	$\alpha_2$ -Adrenoceptor, sedative
Ifosfamide	Anti-cancer, alkylating agent

Data source: (19)

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 to be 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 Day 6/Discharge Confinement to the time of Discharge on Day 90 Visit (Day 91) 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 electronic diary was supplied by the Sponsor and distributed to the subjects by the study site personnel. The product use electronic diary served as a compliance tool in the 3 arms. On Day 6/Discharge Confinement, the compliance to the product was ensured using both the accountability log (from 06:30 AM to time of Discharge) and the product use electronic diary. In case of



discrepancy between the log and the electronic diary entries, the electronic diary was to be considered as the primary source data.

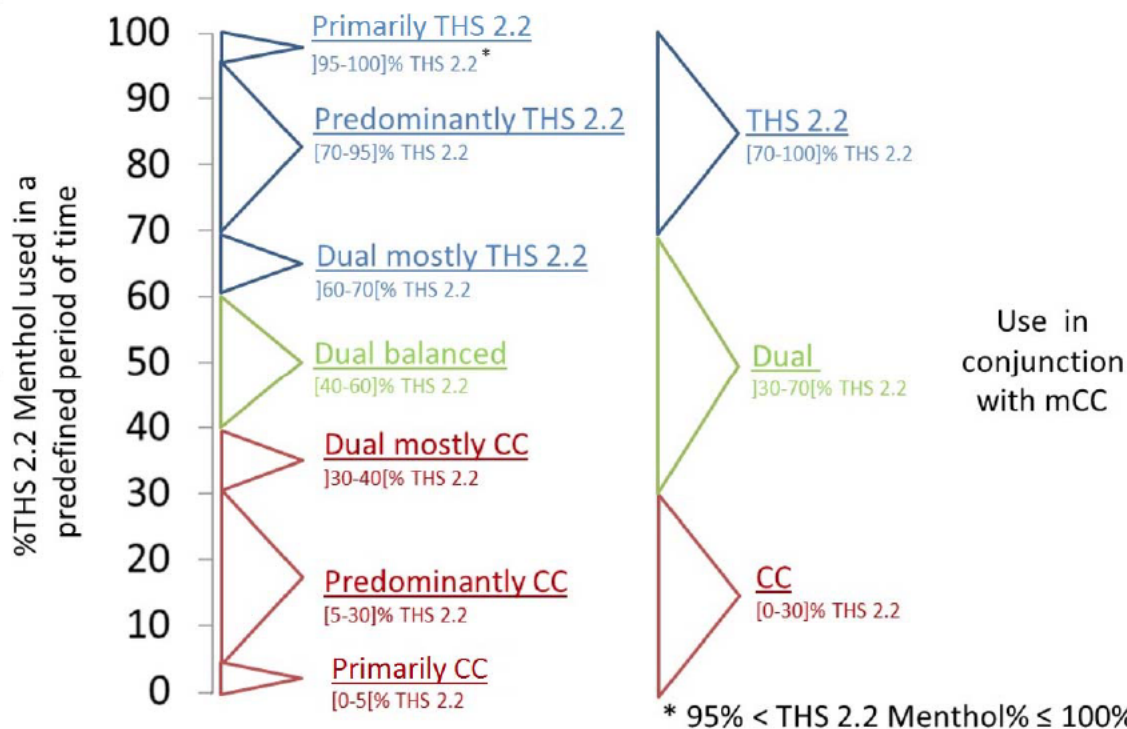
In addition, in the SA arm, compliance was chemically verified using an exhaled CO breath test during both the Confinement and at the Ambulatory Visits. The cut-off point for the CO breath test value to distinguish mCC use versus SA use was 10 ppm (20).

#### 9.4.12.1 Dual-use

Although it was requested that subjects use solely the product allocated to 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 would exclusively use THS 2.2 Menthol, or remain abstinent from smoking, respectively, at all times during the study. Subjects may have concomitantly used THS 2.2 Menthol and CC (dual-use), or smoked some CC in the SA arm.

To assess dual-use of THS 2.2 Menthol and CC, PMI defined dual-use with regards to using THS 2.2 Menthol; calculated as a percentage based on the subject's reported THS Menthol Tobacco Stick consumption and the number of CC smoked (menthol and non-menthol) by study period:

- On Day 30 Visit, using the reported number of CC (menthol and non-menthol) and/or THS Menthol Tobacco Sticks consumption since time of Discharge of Day 6;
- On Day 60 Visit, using the reported number of CC (menthol and non-menthol) and/or THS Menthol Tobacco Sticks consumption after Day 30 Visit; and
- On Day 90 Visit, using the reported number of CC (menthol and non-menthol) and/or THS Menthol Tobacco Sticks consumption after Day 60 Visit.

**Figure 2 Product Use Pattern Categorization**

In the figure above, the more granular categorization scheme was used for the definition of the per protocol population 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 the product (see [Section 11.4.3](#) 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 biomarkers between THS 2.2 Menthol and SA, the confounding effects of the use of any other tobacco/nicotine-containing product (other than the assigned product) needed to be controlled for. Therefore a subject was considered abstinent based on the following categorization:

- “Abstinence”: 100% abstinence from tobacco/nicotine-containing product use other than the assigned product, biochemically verified with CO breath test ≤10 ppm.
- “Predominantly abstinent”: not more than 0.5 uses of any tobacco/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/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 medication was 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.

##### 9.4.13.1 Smoking Restrictions

###### 9.4.13.1.1 Confinement Period

To avoid smoke cross-contamination among the 3 study arms, subjects used THS 2.2 Menthol and smoked mCCs in separate rooms, and the subjects allocated to the SA arm did not have access to the smoking rooms. Precautions were taken to remove cues to smoking 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 the time of Discharge on Day 6. In the mCC arm, subjects were not allowed to use the THS 2.2 Menthol, any nicotine/tobacco-containing products, and mCC other than those 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 site staff.

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

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 after product use.

###### 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. Nicotine replacement 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, Principal Investigator, or site staff.

In the THS 2.2 Menthol and mCC arms, product use was allowed during the Day 30 Visit, Day 60 Visit, and Day 90 Visit.

#### 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) (21).

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 were not permitted (22). In addition, to avoid any effect on the measurement of CYP1A2 activity, alcohol, broccoli, Brussels sprouts, cauliflower, grapefruit, and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana, etc.) were forbidden (11) except for the intake of the caffeine tablet for CYP1A2 measurement. Consumption of quinine-containing drinks (e.g., tonic water) was not allowed.

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. 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.

The fasting state was observed for at least 10 hours prior to blood draws for safety laboratory (Screening, Day 0, Day 6/Discharge Confinement), CREs in serum/plasma/blood (Day 0 and Day 6/Discharge Confinement), serum/plasma bio-banking samples for further analysis of BoExp and CREs (Day 0 and Day 6/Discharge Confinement), blood bio-banking for transcriptomics (Day 0 and Day 6/Discharge Confinement), and oxysterols in plasma (Day 0 and Day 6/Discharge Confinement).

On Day 0 and Day 6/Discharge Confinement, fasting state was observed from at least 30 minutes prior to the collection of buccal and nasal epithelial samples.



#### 9.4.13.2.2 Ambulatory Period

The above dietary restrictions were not applicable for the Ambulatory Period. However, 1 day prior to the Day 90 Visit, and during the visit on site, subjects were asked by the site staff to refrain from consuming grapefruit or grapefruit-containing products, or quinine-containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, chargrilled meat, xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, cocoa, mate, guarana) were not allowed on site during the Day 90 Visit.

A fasting state was observed for at least 10 hours prior to blood draws for safety laboratory (Day 30 Visit [Day 31], Day 60 Visit [Day 61], and Day 90 Visit [Day 91]), risk factor assessments in serum/plasma/blood (Day 30 Visit [Day 31], Day 60 Visit [Day 61], and Day 90 Visit [Day 91]), serum/plasma bio-banking samples for further analysis of BoExp and CREs (Screening Visit, Day 90 Visit [Day 91]), blood bio-banking for transcriptomics (Day 90 Visit [Day 91]), and oxysterols in plasma (Day 90 Visit [Day 91]).

On Day 90 Visit (Day 90), fasting state was observed from at least 30 minutes prior to collection of nasal epithelial and buccal samples.

### 9.5 Study Variables Assessed and Schedule of Events

Personnel performing study measurements or recordings had appropriate training which was fully documented and QC measures were in place. An overview of all study procedures is shown in the Schedule of Events ([Table 8](#)).

Due to logistical reasons, it was not reasonable for all subjects to undergo a procedure at the same time, therefore adequate time windows were given for each study procedure and each time point (see Section 9 of the protocol [[Appendix 16.1.1](#)]). Site personnel adhered to the site's Standard Operating Procedures (SOPs) for all activities.

#### 9.5.1 Biomarker Assessments

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

##### 9.5.1.1 Biomarkers of Exposure

###### 9.5.1.1.1 Urinary Biomarkers of Exposure

The following BoExp were measured in 4-hour and 24-hour urine collection samples as per [Table 9](#) and [Table 10](#), respectively:

- BoExp, primary objective: MHBMA, 3-HPMA, S-PMA, and Total NNAL.





- BoExp, secondary objective: Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, NEQ, CEMA, B[a]P, HEMA, S-BMA, and HMPMA.

Urinary BoExp were measured in 24-hour urine samples during the Confinement Period from Day 0 onwards to Day 5, and during the Ambulatory Period at the Day 30 Visit, at the Day 60 Visit, and at the Day 90 Visit. In [Table 8](#), the dot corresponds to the day on which the 24-hour urine collection period started. For example, for NEQ measured on Day 5 in the 24-hour urine, collection started on Day 5 and ended 24 hours later on Day 6/Discharge Confinement. At time of Discharge on Day 6/Discharge Confinement, 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 8](#).

Additionally, BoExp were measured in 4-hour urine fractions during the Confinement Period on Day -1 and during the Ambulatory Period at the Day 90 Visit (Day 91/Discharge Ambulatory). On Day -1, each subject emptied his/her bladder shortly before 10:00 AM, and the volume of urine collected was discarded. The collection started at 10:00 AM  $\pm$  30 minutes (empty bladder) and ended 4 hours later at 02:00 PM  $\pm$  30 minutes. At the Day 90 Visit (Day 91/Discharge Ambulatory), the 4-hour fraction started immediately after the end of the 24-hour urine collection (the start of 4-hour fraction corresponded to the end of 24-hour collection).

For normalization of BoExp, creatinine was also measured in the 24-hour urine and 4-hour urine samples.

#### 9.5.1.1.2 Exhaled CO and COHb

Carboxyhemoglobin measured in blood and exhaled CO was investigated as a measure of exposure to CO in all 3 study arms. A CO breath test was conducted in timely conjunction with the blood sampling for COHb, where applicable. In the SA arm, the CO breath test served as a verification of compliance during the Confinement Period and Ambulatory Visits ([Section 9.4.12](#)).

##### Carbon Monoxide Breath Test:

Carbon monoxide in exhaled breath was measured using the Micro+™ Smokerlyzer® device in all 3 study arms.

During the Confinement Period on Day -1 to Day 5 for subjects in the THS 2.2 Menthol and CC arms, the CO breath test was conducted 4 times per day. The first assessment 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-09:30 PM.

For subjects in the SA arm from Day 1 onwards, the first CO breath test was performed between 08:00 AM and 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-09:30 PM.





For all subjects on Day -2 and Day 6/Discharge Confinement, 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 from Day -1 until Day 6/Discharge Confinement.

On Day -1, and from Day 1 to Day 4: one blood sample was collected in the evening between 08:00 PM and 09:30 PM.

On Day 0, two blood samples were collected: one blood sample was collected prior to the gas transfer assessment and prior to product use (the COHb levels measured served for adjustment of gas transfer values only). The second blood sample was collected in the evening between 08:00 PM and 09:30 PM.

On Day 5: for THS 2.2 Menthol and mCC arms, one blood sample was collected within 15 minutes prior to 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.

On Day 6/Discharge Confinement: one blood sample was collected prior to the gas transfer assessment for all subjects, and prior to product use for THS 2.2 Menthol and mCC arms (the COHb levels measured served for adjustment of gas transfer values only).

For subjects in the SA arm from Day 1 onwards, the first COHb was performed between 08:00 AM and 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, one blood sample was collected during the visit, irrespective of the time of product use.

One blood sample was collected on Day 91/Discharge Ambulatory prior to gas transfer assessment for all subjects, and prior to product use for THS 2.2 Menthol and mCC arms (the COHb levels measured served for adjustment of gas transfer values only).

#### 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/Discharge Confinement 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 and 09:30 PM.

Blood samples for nicotine/cotinine PK profiling on Day 5 and Day 6/Discharge Confinement 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 ( $T_0$ ) served as reference for the time to peak concentration ( $t_{peak}$ ). 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  $T_0$ . On Day 6/Discharge Confinement, 2 blood samples were drawn. The first one was 20 hours after  $T_0$  and the second blood sample was 24 hours after  $T_0$  (with  $T_0$  being the start time of first product use on Day 5).

On Day 5 and Day 6/Discharge Confinement (SA arm only); on Day 5, one blood sample was drawn in the evening between 08:00 PM and 09:30 PM and on Day 6/Discharge Confinement, one blood sample was drawn in the morning between 08:00 AM and 09:30 AM.

At the Day 30 Visit, Day 60 Visit, and 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, HDL, TG, TC, HbA1c, sICAM-1, WBC (leukocytes) count, Apo A1, Apo B, 8-epi-PGF<sub>2α</sub>, 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 (leukocytes), 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 assessments which required blood, serum, or plasma:



- Systolic and diastolic blood pressure: on Day 0, Day 6/Discharge Confinement, Day 30, Day 60, and Day 91/Discharge Ambulatory. The results from vital signs assessments were used.
- hs-CRP, homocysteine, blood glucose, LDL-C, HDL-C, TG, TC in serum: on Day 0, Day 31, Day 61, and Day 91/Discharge Ambulatory. Sample collection was planned to measure hs-CRP, homocysteine, LDL-C, and HDL-C at the mentioned time points. The results for blood glucose, TG, and TC from the safety laboratory panel on Day 0, Day 31, Day 61, and Day 91/Discharge Ambulatory were used.
- Fibrinogen in plasma: on Day 0, Day 31, Day 61, and Day 91/Discharge Ambulatory.
- HbA1c in serum: Day 0 and Day 91/Discharge Ambulatory.
- Apo A1 and Apo B in serum: on Day 0, and Day 90 Visit.
- sICAM-1 in serum: on Day 0, Day 6/Discharge Confinement, Day 31, Day 61, and Day 91/Discharge Ambulatory.
- 8-epi-PGF<sub>2α</sub> and 11-DTX-B2: in 24-hour on Day 0, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit, and in 4-hour urine fractions on Day 91/Discharge Ambulatory. The results were normalized to creatinine and expressed as concentrations adjusted for creatinine.
- WBC (leukocytes) and platelet count in whole blood: on Day 0, Day 6/Discharge Confinement, Day 31, Day 61, and Day 91/Discharge Ambulatory. The results from the safety laboratory panel were used.
- Waist circumference and weight: evaluated on Day -2 and on Day 91/Discharge Ambulatory as part of the clinical examination.

#### 9.5.1.2.2 CYP1A2 Activity Test

Cytochrome P450 1A2 activity was assessed in plasma on Day 0, Day 5, and Day 90 by measuring PX and CAF concentrations and calculating the PX/CAF molar metabolic ratio (11). Blood samples to measure PX and CAF were drawn approximately 6 hours ( $\pm 15$  minutes) after the intake of one “Vivarin” caffeine tablet (around 200 mg caffeine) with 240 mL  $\pm 10$  mL water (11).

The exact time of intake of the caffeine tablet in the morning, and of the blood sample (6 hours [ $\pm 15$  minutes] after intake of the tablet) were recorded.

#### 9.5.1.2.3 CYP2A6 Activity Test

Cytochrome P450 2A6 activity was measured in plasma on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory, using the molar metabolic ratio of *trans*-3'-hydroxycotinine to cotinine (23). Blood sampling for CYP2A6 was performed prior to first 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 performed in 1 bacterial strain (*S. typhimurium* strain YG1024), using S9 metabolic activation and 4 doses for each of the urine extracts.

#### 9.5.1.2.5 Oxysterols

Oxysterols were measured in plasma following at least 10 hours of fasting on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory using a non-validated method.

Oxysterols

included:

6 $\alpha$ -hydroxy-5 $\alpha$ -cholestane, 7 $\alpha$ -hydroxycholesterol, 5 $\alpha$ ,6 $\alpha$ -epoxycholestanol, 7-ketocholesterol, 7 $\beta$ -hydroxycholesterol, 5 $\beta$ ,6 $\beta$ -epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol; in addition to TC. Based on the outcome of the study, it was determined whether the assay required further validation.

### 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); ECG data; clinical chemistry, hematology, concomitant medications, urinalysis safety panel, and physical examination (including BMI).

#### 9.5.2.1 Adverse Events

The FDA MRTP guideline (4) provides the following definition for AEs for tobacco products: “an AE is any health-related event associated with the use of a tobacco product in humans, which is adverse or unfavorable, whether or not it is considered tobacco-product related”.

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

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

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





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

Any pre-planned hospitalizations that were known at the time of signing the ICF were not recorded as SAEs; however they were recorded as AEs only. Any AEs that occurred during this pre-planned hospitalization were 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 obtaining, assessing, and documenting all AEs during the study. AE information was collected and recorded from the time of signature of the ICF onwards until EOS via spontaneous reporting, or by the use of consistent, open, non-directive questions from study site staff (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 face-to-face interviews with the subject; in addition, AE information might have emerged from the review of subject questionnaires and 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 and/or SAEs were assessed by the Principal Investigator or designee as either ‘related’ or ‘not related’ to IP and/or study procedures according to the following definitions:

- Not related: The temporal relationship of the clinical event to IP administration or 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 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 were not consistent with information already known about the IP, 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 discontinuation are provided in the protocol ([Appendix 16.1.1](#)).

Any occurrences of malfunction of the THS Tobacco Stick Holder or THS Charger were documented by the Principal Investigator using a device issue log. Furthermore, any malfunctions of the THS Tobacco Stick Holder or THS 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 from the clinic on Day 6/Discharge Confinement, and on Day 30, Day 60, and Day 91/Discharge Ambulatory. Appropriate medical advice was provided to the subject in case of any medical findings requiring health care.

Body height was measured at Screening only. Waist circumference was measured on Admission (Day -2) and on Day 91/Discharge Ambulatory. 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 Day 91/Discharge Ambulatory). All measurements were made after the subject had rested for at least 5 minutes in a supine position and at least 15 minutes after smoking/product use. For every measurement, it was documented if the subject had smoked within 15 minutes prior to the measurement.



#### 9.5.2.4 Clinical Laboratory Parameters

Hematology, clinical chemistry and urinalysis for the safety panel were measured at Screening, Day 0, Day 6/Discharge Confinement, Day 31, Day 61, and Day 91/Discharge Ambulatory. Blood samples were taken after at least 10 hours of fasting (Section 9.4.13.2). The urine test was performed semi-quantitatively as a urine dipstick test. Parameters to be measured are listed in Table 6. The methodology for measuring albumin changed during the study. Further details are provided in a letter of clarification (Appendix 16.1.1, Section 16.1.1.3).

**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 (ALT)	Nitrite
Mean corpuscular volume	Aspartate aminotransferase (AST)	Red blood cell traces
Platelet count	Blood urea nitrogen	Protein
Red blood cell count	Creatinine	Specific gravity
White blood cell (WBC) count	Gamma-glutamyl transferase (GGT)	
Differential WBC count:	Fasting glucose	
Neutrophils	Lactate dehydrogenase	
Basophils	Potassium	
Eosinophils	Sodium	
Lymphocytes	Total bilirubin	
Monocytes	Direct bilirubin	
	Total cholesterol	
	Triglycerides	

#### 9.5.2.5 Electrocardiogram

A standard 12-lead ECG was recorded at Screening, on Day 6/Discharge Confinement, Day 30, Day 60, and Day 91/Discharge Ambulatory. The ECG testing was performed after the subject had rested for at least 5 minutes in a supine position, and as per the site's local practice.

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 and Fridericia's formula. Every ECG was assessed as normal, abnormal – clinically not relevant, or abnormal – 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 on the Day of Admission (Day -2). The urine was screened for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

#### 9.5.2.7 Breath Alcohol Test

Subjects underwent urine or breath alcohol testing at the Screening Visit and at Admission to the clinic (Day -2).

#### 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 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), and on Day 6/Discharge Confinement, Day 30, Day 60, and Day 91/Discharge Ambulatory. Female subjects with a positive pregnancy test at the Screening Visit or on Day -2 were considered a screening failure and were 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 or designee informed the subject about the risks associated with smoking during pregnancy.

Post-menopause is formally defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation). If a woman claimed she was post-menopausal, but had menstruated within 12 months, a follicle-stimulating hormone test was performed and the subject was included only if the result was within acceptable limits.





All 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, hepatitis C virus, and HIV1/2 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 in order to confirm the subject's smoking status. The test detected cotinine with a threshold of  $\geq 200$  ng/mL.

##### 9.5.3.2 Chest X-ray

A chest X-ray (anterior-posterior and left lateral views) was assessed during the Screening Period to exclude subjects with relevant pulmonary diseases. Subjects were referred to a radiology facility for this procedure. No new examination was required if the subject 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 to Assess Full Lung Functions

The full lung function tests were performed prior to first product use (mCC or THS 2.2 Menthol) on Day 0 (baseline values), Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory. The subject was required to be at rest for at least 15 minutes prior to lung function testing. All lung function maneuvers were recorded with the subject in a sitting position throughout the study.

Full lung function tests included the recording of FEV<sub>1</sub>, FVC, the ratio FEV<sub>1</sub> to FVC, and MEF 25-75 (using spirometry with bronchodilator), lung volumes (VC, TLC, and IC) using the helium dilution technique, and the DLCO and KCO (using the single breath technique for CO). The assessments were performed in the following sequence:

1. Gas transfer (DLCO, KCO).
2. Lung volume (VC, TLC, and IC).
3. Spirometry with bronchodilator.

All personnel performing full lung function testing were appropriately trained, and QC measures were put into place and properly documented and filed at the pulmonary function laboratory (including the records of the calibration, if applicable). A certified respiratory therapist performed the assessment and the results were assessed by a pulmonologist.



For full lung functions, the following were performed:

1. The ambient temperature, barometric pressure, and humidity were measured and entered into the software of the instrument.
2. The instrument was calibrated prior to each subject's test.
3. The subject wore a nose clip.
4. The subject was asked to place the mouthpiece in their mouth and breathe normally. They were then instructed to inhale to TLC and exhale as hard and as fast as they possibly could until they reached FRV. At this point they were instructed to inhale as hard and as fast as possible until they were back to TLC.

#### 9.5.3.3.1 Spirometry With and Without Bronchodilator

The following recommendations were followed:

1. The instrument was calibrated prior to the procedure.
2. The subject was instructed to take a full inspiration away from the cardboard mouthpiece, seal his/her lips around the mouthpiece (making sure that his/her tongue did not occlude the mouthpiece), and perform an expiratory maneuver.
3. The subject was instructed to do the following: breathe out as rapidly and forcefully into the mouthpiece as possible and continue until he/she felt his/her lungs were completely empty.

##### Spirometry Without Bronchodilator

Spirometry was conducted without bronchodilator at Screening only. Values for FEV<sub>1</sub>, FVC, the ratio FEV<sub>1</sub> to FVC, and MEF 25-75 were recorded.

The spirometry without bronchodilator was performed prior to the spirometry with bronchodilator and at least 1 hour after smoking.

##### Spirometry With Bronchodilator

At the Screening Visit, on Day 0, on Day 6/Discharge Confinement, and on Day 91/Discharge Ambulatory, spirometry with bronchodilator was performed and post-bronchodilator values for FEV<sub>1</sub>, FVC, the ratio FEV<sub>1</sub> to FVC, and MEF 25-75 were recorded.

The spirometry was performed in all subjects 15-30 minutes post administration of around 400 µg salbutamol (usually equivalent to 2-4 puffs assuming 90 µg/puff).

The results from FEV<sub>1</sub>, and the ratio FEV<sub>1</sub> to FVC at Screening were used for eligibility criteria.



#### 9.5.3.3.2 Lung Volume Measurements (VC, TLC, and IC)

Lung volume measurements (VC, TLC, and IC) were conducted as part of the full lung function tests on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory, and the following values were recorded: VC, FRV, IC, and TLC values.

The helium dilution technique was a closed-circuit system where a spirometer was filled with a mixture of helium and oxygen. The closed-circuit rolling seal spirometer was filled to a starting volume of 6 liters with a mixture containing helium, oxygen, and balance room air. Oxygen was set to 30% so that all test subjects were comfortable; exact content was analyzed. The subject was asked to seal their lips around the mouthpiece and breathe normally on the closed-circuit while the helium mixed and equilibrated. During this time carbon dioxide was removed by a chemical absorber and oxygen was automatically replaced. Once equilibration had occurred, the subject was asked to perform one or more VC efforts to end the test.

#### 9.5.3.3.3 Gas Transfer (DLCO and KCO)

This procedure was conducted as part of the full lung function tests on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory using the single breath technique. DLCO and KCO (DLCO to alveolar volume [VA] ratio) values were recorded.

Blood sampling for COHb measurement was performed prior to the gas transfer assessments to adjust gas transfer values to COHb levels.

The subject was asked to seal their lips around the mouthpiece, with a nose clip on the nose. They were then asked to breathe room air for a few tidal breaths.

The subject was then instructed to:

1. Inhale as far as possible. This was estimated as at least 90% of the subject's VC.
2. Hold their breath for 10 s without straining. The subject relaxed against the shutter and was encouraged not to breath out or breath in against it, as this would have altered the intrathoracic pressure and the pulmonary hemodynamics, resulting in either an increase (breathing in) or decrease (breathing out) in DLCO.
3. Blow as far as possible.
4. On completion of the maneuver, the subject was rested in a sitting position, before repeating the test a minimum of 2 times. The time between maneuvers was at least 4 minutes.

#### 9.5.3.4 Demographic Data

Demographic data (sex, date of birth/age, ethnicity, and race) 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 done at the Screening Visit and on Day -2. At the Screening Visit, smokers were asked to bring a pack of their current mCC brand(s) to the site. On Day -2, subjects handed their mCC supply for the entire Confinement Period to the site staff and site staff documented the brand name. A photograph of the front and the side of the cigarette pack supplied by the subject was taken by the study site staff in addition to recording the brand name. These photographs were considered as source documentation. A copy of the photographs was provided to the Sponsor electronically on Compact Discs.

#### 9.5.3.6 Smoking History, Willingness to Quit, and Intention 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. This self-reported mCC daily consumption was used for eligibility. 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 on the Day of Admission (Day -2), subjects were also asked if they were ready to abstain from smoking for up to 91 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.

Intention to quit smoking was assessed at Screening, Day -2, Day 30, Day 60, and Day 90 by the means of Prochaska 'Stage of Change' questionnaire see [Section 9.5.6.4.9](#). Only smokers who were in the precontemplation stage (who were not willing to quit within the next 6 months) were enrolled 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 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 up to 3 THS Menthol Tobacco Sticks). In female subjects, the THS 2.2 Menthol test 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 after enrollment on Day -2:

"Which product would you prefer to be randomized to: THS 2.2 Menthol, mCC, SA, or no preference (NP)."

If the subject preferred to be randomized to SA arm, then, the Prochaska 'Stage of Change' questionnaire was re-administered. If the subject planned to quit within 6 months, the subject was discontinued from the study.

### 9.5.4 Bioanalytical Methods

All bioanalytical assays and laboratory assessments except the assay to measure oxysterols were carried out using validated methods as documented in the bioanalytical report ([Appendix 16.1.8](#)). Precautions were taken during blood sampling and processing to prevent the contamination of samples with environmental smoke. Of note, WBC (leukocytes), 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 laboratories details are provided in [Section 6](#).

### 9.5.5 Sample Collection Storage and Shipping

Samples were tested as described in [Section 6](#) by Celerion, with the exception of COHb blood samples, and the safety laboratory panel at Screening only which were tested at local laboratories ([Section 6](#)). Blood (serum and plasma) and urine samples for bio-banking of were shipped to (b)(4). The samples for measurement of oxysterols were tested at PMI Research and Development Laboratory, Neuchâtel, Switzerland. The urine test for the safety laboratory, urine pregnancy tests, urine drug screen, and urine cotinine tests were performed by personnel at the study sites.

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

Venous 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 310 mL, which included 40 mL for safety and repeated analysis, 30 mL of blood 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 were given, see [Section 5.4](#)). The blood samples for transcriptomics and the data related to these samples were anonymized and are the subject of a separate report.

#### 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 Confinement Period: subjects emptied their bladders shortly before 06:30 AM on the study day indicated in [Table 8](#) and discarded the urine. The collection period was started at 06:30 AM  $\pm$  30 minutes and ended the following day at 06:29 AM  $\pm$  30 minutes. 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 time of Discharge on Day 6, subjects emptied their bladder shortly before 06:29 AM. This was the last urine collection for the 24-hour urine for the Day 5 dot mark in [Table 8](#).

For 24-hour urine collection during Ambulatory Period: the 24-hour urine fraction was collected at the Day 30 Visit, Day 60 Visit, and Day 90 Visit. Subjects were asked to arrive at the site in the morning on Day 30, Day 60, and Day 90, and remained overnight until Day 31, Day 61, and Day 91/Discharge Ambulatory, respectively. Subjects were asked to empty their bladder on Day 30, Day 60, and Day 90 shortly before 09:00 AM (this urine was discarded). The collection period started at 09:00 AM  $\pm$  30 minutes and ended on the following day. After nearly 24-hours of collection at 08:59 AM  $\pm$  30 minutes, the subjects emptied their bladder again and this urine was used as the final collection of the 24-hour urine sample.

For 24-hour urine collection during both Confinement and Ambulatory Periods: during the sampling period, all urine passed 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 to be passed into the toilet. The volume of 24-hour urine, and the start and the end time of urine collection were recorded by the study site staff.

For assessment of urine BoExp, creatinine for normalization of urine BoExp, 8-epi-PGF<sub>2 $\alpha$</sub>  and 11-DTX-B2, sample bio-banking, and urine mutagenicity; aliquots from the 24-hour urine collection were taken.

For the 4-hour urine collection on Day -1 and Day 91/Discharge Ambulatory: a 4-hour urine fraction was collected for each subject on Day -1 and on Day 91/Discharge Ambulatory. On Day -1, each subject emptied his/her bladder shortly before 10:00 AM, and the volume of urine collected was discarded. The collection started at 10:00 AM  $\pm$  30



minutes (empty bladder) and ended 4 hours later at 02:00 PM  $\pm$  30 minutes. On Day 91/Discharge Ambulatory, the 4-hour fraction started immediately after the end of the 24-hour urine collection (the start of 4-hour fraction corresponded to the end of the 24-hour collection). The volume of the 4-hour urine fraction and the start and end time of urine collection were recorded by the study site staff.

Details regarding the processing of the 4-hour and 24-hour urine samples were provided in a separate Celerion sample handling manual.

#### 9.5.5.3 Bio-banking

Samples collected for bio-banking were collected only after 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 collection) and serum/plasma were collected as follows:

- Samples were collected from the 24-hour urine collections that started on Day 0, Day 5, and Day 90 (10 tubes of 10 mL each per time point).
- Serum/plasma was collected on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory (30 mL of blood in total with  $2 \times 5$ -mL tubes of blood drawn per time point: from one tube,  $2 \times 1$ -mL samples of serum and plasma were collected and stored).

If a subject gave consent for sample bio-banking of whole blood for further transcriptomics analysis, blood was collected on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory (5 mL per time point, which was split further 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 (b)(4). After the final 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 was stored for a maximum of 5 years.

If a subject gave consent for sample bio-banking to collect and store samples from nasal epithelial and buccal collections, samples were collected on Day 0, Day 6/Discharge Confinement, and Day 90. Site personnel were trained to follow the procedures which are defined in the protocol ([Appendix 16.1.1](#)). If the subject wanted to have their nostril numbed prior to nasal epithelial collection, site staff investigated whether the subject had any allergy to lidocaine. The samples and all related data were anonymized and are the subject of a separate report. The nasal epithelial and buccal samples were stored for a maximum of 5 years.





## 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 NRT products, or the use of other nicotine/tobacco-containing products. All subjects (including those subjects randomized to the SA arm) were required to complete this diary on a daily basis from the time of Discharge on Day 6 until the time of Discharge on Day 91/Discharge Ambulatory. Subjects were trained by site staff in the use of this electronic diary during the Confinement Period at the time the diary was delivered to the subject.

### 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 using the HST SODIM<sup>®</sup> portable device. The HST SODIM<sup>®</sup> device, model SPA/M (SODIM<sup>®</sup> 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 THS Menthol Tobacco Stick being smoked/used. The Holder was connected by 2 narrow tubes to a portable data logger/recording system.

On Day 0, the HST SODIM<sup>®</sup> device was used for all mCC smoked for all subjects. On Day 1 and Day 4 of the Confinement Period, the HST SODIM<sup>®</sup> device was used for every smoking/product use 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 assessment started between 08:30 and 09:30 AM and every mCC or THS Menthol Tobacco Stick used in the following 4-hour window was assessed.

Smoking topography with the HST SODIM<sup>®</sup> device were not done in subjects smoking mCC that were incompatible with the HST SODIM<sup>®</sup> device (e.g., slim mCC), and for subjects in the SA arm, no HST assessments were performed.

For each subject applicable, one HST SODIM<sup>®</sup> 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). An HST SODIM<sup>®</sup> device was assigned to all subjects smoking mCCs which were compatible with the HST SODIM<sup>®</sup> device.

The Sponsor provided training on the use of the HST SODIM<sup>®</sup> device to the study site staff. The study site staff, in turn, provided training to the subjects. All HST SODIM<sup>®</sup> devices were returned to the Sponsor after completion of the study.





The HST SODIM<sup>®</sup> device measured and recorded the flow and other per-puff parameters listed in [Table 20](#). From these parameters, per-cigarette parameters shown in [Table 21](#) 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 THS Tobacco Plugs collected during the study were sent to the Sponsor for subsequent visual inspection to determine whether combustion had occurred during product use.

#### 9.5.6.4 Questionnaires

The subject questionnaires and the VAS used in this study were entered by the subject directly in an ePRO device or on paper copy. All subject reported outcome data was provided in English or Spanish and instructions were provided in the subject's local language. The questionnaires and the VAS were reviewed for completeness by the study site staff and subjects were requested to complete any missing information.

Symptoms or worsening of symptoms documented on any of the questionnaires or the VAS did not need to be documented as additional AEs because the questionnaires 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 site staff, using open, non-directive questions ([Section 9.5.2.1](#)).

##### 9.5.6.4.1 Fagerström Test for Nicotine Dependence

Potential nicotine dependence was assessed via a questionnaire at Screening and on Day 90 using the FTND in its revised version ([24](#)).

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) ([25](#)).

##### 9.5.6.4.2 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 on Day 31, Day 61, and Day 91/Discharge Ambulatory. From Day 0 to Day 6/Discharge Confinement only, assessment of cough was performed prior to the



start of product use/smoking and no later than 10:00 AM. On Day 31, Day 61, and Day 91/Discharge Ambulatory, assessment of cough was conducted irrespective of the time of product use 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. The VAS ranged from 'not bothering me at all' to 'extremely bothersome'.

Furthermore, subjects assessed the intensity and frequency of cough and the amount of sputum produced during the previous 24 hours on Likert scales ([Table 7](#)).

**Table 7 Likert Scales for the Assessment of Cough**

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 to share any other important observations with the site staff 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](#)).

#### 9.5.6.4.3 Modified Cigarette Evaluation Questionnaire

Product evaluation was assessed using the MCEQ ([26](#)). 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 on every Ambulatory Visit on Day 30, Day 60, and Day 90. On Day -1 and Day 0, all 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.

#### 9.5.6.4.4 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 (27). The QSU-brief is a self-reported questionnaire with 10 items to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicated a higher urge-to-smoke.

The QSU-brief was completed by the subject 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.

#### 9.5.6.4.5 Minnesota Nicotine Withdrawal Scale

The MNWS-R version is a valid and reliable scale that has been used previously to examine signs and symptoms of withdrawal from cigarette smoking (28, 29). 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 was filled in by the subject. Furthermore, the subject's weight was not recorded for the purpose of the MNWS-R. 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-R was completed on a daily basis from Day 0 to Day 6/Discharge Confinement, and at every visit during the Ambulatory Period, i.e., Day 31, Day 61, and Day 91/Discharge Ambulatory. From Day 0 to Day 6/Discharge Confinement only, MNWS-R questionnaires were asked prior to the start of product use/smoking and no later than 10:00 AM. On Day 31, Day 61, and Day 91/Discharge Ambulatory, assessment of MNWS-R was conducted irrespective of the time of product use but no later than 10:00 AM.





#### 9.5.6.4.6 Human Smoking Topography Questionnaire

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

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

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

#### 9.5.6.4.7 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.

At Screening the subjects were informed in detail about the exams and evaluations planned during the study, and similarly notified about the SES assessment which would be performed on Day 4 once they provided informed consent and were enrolled into the study.

On Day 4, subjects filled in a questionnaire, which allowed the Sponsor to determine the subject's SES. Subjects were asked a series of questions related to their education, occupational status, and size and annual income of their household. These data were used to create a measure for SES that categorizes subjects into low, moderate, and high SES (30). The method used to create SES tertiles is described in the SAP ([Appendix 16.1.8](#)). If the subject did not want to answer the questionnaire, they were not discontinued from the study.

#### 9.5.6.4.8 Current and Past Smoking Behavior

Subjects were assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by the means of 2 questionnaires. The questionnaires were asked in the following sequence:

1. A standard questionnaire (Behavioral Risk Factor Surveillance System Questionnaire 2011) (31) which was validated.
2. A smoking questionnaire (SQ) which was to be validated. Immediately after the administration of the SQ, some supplemental questions were collected on the completion of the SQ questionnaire.





The Behavioral Risk Factor Surveillance and the SQ were self-administrated and to be answered by subjects. The supplemental questions were asked by the site.

The standard questionnaire is the questionnaire used in the Behavioral Risk Factor Surveillance System Questionnaire 2011 (31), Section 7 on tobacco use. The standard questionnaire consists of 5 questions. All 5 questions are close-ended questions and the responses are exhaustive and mutually exclusive:

- Question 1 collects information on the 100 cigarettes criterion.
- Question 2 allows for a broad classification of current cigarette smoking behavior (daily, occasional, non).
- Question 3 captures quitting experience during past 12 months.
- Question 4 records past smoking duration.
- Question 5 provides information regarding other tobacco use, e.g., smokeless tobacco.

The SQ focuses on self-reported current and past cigarette smoking behavior. The SQ consists of 8 questions. The first 3 questions are close-ended questions and the responses are exhaustive and mutually exclusive. The last 5 questions refer to the individual smoking history and are answered to the degree applicable.

- Question 1 allows for a broad classification of current cigarette smoking behavior (daily, occasional, ex, non).
- Questions 2 and 3 collect information on the 100 cigarettes criterion and on ever smoking (defined as smoking at least one cigarette per day).
- Question 4 captures age of initiation and Questions 5 and 6 capture the current as well as total quitting duration, respectively.
- Question 7 captures the predominantly smoked brand of cigarettes in the last 12 months of smoking.
- Question 8 captures the tobacco smoking history. Daily numbers of manufactured cigarettes, as well as hand-rolled cigarettes, cigars, and pipes consumed, separately for 7 time periods.

Finally, the supplemental questions consist of 8 questions.

- Supplemental question 1 is related to the time which the subject spends to complete the SQ.
- Supplemental questions 2-7 are close-ended questions and are to be answered yes or no.
- Supplemental question 8 is open-ended, allowing for addition comments provided by subjects.

The daily mCC consumption reported in these questionnaires was not used for eligibility. The data from these questionnaires were described as part of the CSR and further analysis is the subject of a separate report.



#### 9.5.6.4.9 Prochaska 'Stage of Change' Questionnaire: Intention to Quit Smoking

The Prochaska 'Stage of Change' questionnaire was used to assess the smokers' mental state for the intention to quit (32, 33) at Screening (prior to product trial) and on Day -2, Day 30, Day 60, and Day 90.

There are 5 stages of change describing smokers and former smokers:

1. Precontemplation
2. Contemplation
3. Preparation
4. Action
5. Maintenance

In the precontemplation stage, the individual does not recognize smoking as a problem. In the contemplation stage, the individual is gathering information about smoking, such as contacting a health care provider, or tobacco quit line for information on the effects of smoking or cessation classes. During this stage, the stress and inconvenience of quitting smoking is greater than the immediate and possible long-term health effects from continued smoking. In the preparation stage, intention and behavior begin to come together and the subject is preparing to enter the action stage in the next 30 days. It is necessary for the subject to recognize the benefits of not smoking before a subject can enter the action stage, and as a result, change their smoking behavior. After 6 months of not smoking, the individual reaches the maintenance stage when different skills may be needed to prevent relapse from those employed in the initial behavior change.

#### 9.5.7 Schedule of Events

Table 8 presents the Schedule of Events for the entire study period.



**Table 8 Schedule of Events**

	Screening	Confinement Period									Ambulatory Period						Safety Follow-up <sup>2</sup>
											Day 30 Visit ± 5 days		Day 60 Visit ± 5 days		Day 90 Visit ± 5 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6 <sup>y</sup>	30	31	60	61	90	91	91 to 119
Informed consent for study participation and two informed consents for bio-banking	•																
Admission/Discharge		•								•						•	
Information on the risk of smoking/smoking cessation advice and debriefing	•	•								•		•		•		•	
Monitoring/intensive support for SA arm					•	•	•	•	•	•	•	•	•	•	•	•	
Inclusion/exclusion criteria	•	•															
Enrollment		•															
Randomization				•													
Demographics, medical history	•																
Concomitant diseases	•	•															
Socio-economic questionnaire								•									
Vital signs <sup>a</sup>	•	•	•	•	•	•	•	•	•	•	•		•			•	
Physical examination	•	•								•	•		•			•	



	Screening	Confinement Period								Ambulatory Period							Safety Follow-up <sup>2</sup>
											Day 30 Visit ± 5 days		Day 60 Visit ± 5 days		Day 90 Visit ± 5 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6 <sup>y</sup>	30	31	60	61	90	91	91 to 119
Body height and weight <sup>b</sup>	•	•								•	•		•			•	
Waist circumference <sup>c</sup>		•														•	
Spirometry <sup>d</sup>	•			•						•						•	
Prior/concomitant medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
B/U: Hematology, clinical chemistry, urine analysis <sup>e</sup>	•			•						•		•		•		•	
Electrocardiogram	•									•	•		•			•	
Chest X-ray <sup>f</sup>	•																
B: HIV, hepatitis B and C	•																
Urine cotinine screening test	•																
U: Urine drug screen	•	•															
U: Pregnancy test	•	•								•	•		•			•	
Alcohol urine or breath test	•	•															
FTND	•														•		
Smoking history	•	•															
Intention to quit smoking in the next 6 months (Prochaska ‘Stage of Change’ questionnaire)	•	•									•		•		•		





	Screening	Confinement Period									Ambulatory Period						Safety Follow-up <sup>2</sup>
											Day 30 Visit ± 5 days		Day 60 Visit ± 5 days		Day 90 Visit ± 5 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6 <sup>y</sup>	30	31	60	61	90	91	91 to 119
Readiness to comply with study protocol: to abstain from smoking for up to 91 days	•	•															
Identification of mCC	•	•															
THS 2.2 Menthol demonstration	•																
THS 2.2 Menthol product test and readiness to use the product <sup>g</sup>		•															
Question on product preference		•															
Collection of mCC butts for accountability			•	•	•	•	•	•	•	•							
Collection tobacco plugs of used THS Menthol Tobacco Sticks for further analysis					•	•	•	•	•		•		•		•		
Collection of empty/partially used THS Menthol Tobacco Stick packs for accountability											•		•		•		
CO breath test <sup>h</sup>		•	•	•	•	•	•	•	•	•	•		•		•		



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[illegible]



	Screening	Confinement Period								Ambulatory Period						Safety Follow-up <sup>z</sup>	
											Day 30 Visit ± 5 days		Day 60 Visit ± 5 days		Day 90 Visit ± 5 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6 <sup>y</sup>	30	31	60	61	90	91	91 to 119
fraction: 8-epi-PGF <sub>2α</sub> and 11-DTX-B2																	
One caffeine tablet (200 mg caffeine)				•					•						•		
B: CYP1A2 activity				•					•						•		
B: CYP2A6 activity				•						•						•	
B: Oxysterols				•						•						•	
Product use diary <sup>o</sup>										•	•	•	•	•	•	•	
QSU-brief questionnaire <sup>p</sup>			•	•	•	•	•	•	•		•		•		•		
MNWS (revised version) <sup>q</sup>				•	•	•	•	•	•	•		•		•		•	
MCEQ (modified version; THS 2.2 Menthol and mCC arms) <sup>r</sup>			•	•	•	•	•	•	•		•		•		•		
HST (THS 2.2 Menthol and mCC arms) <sup>s</sup>				•	•			•			•		•		•		
HST questionnaire				•				•			•		•		•		
Assessment of cough <sup>t</sup>				•	•	•	•	•	•	•		•		•		•	
Risk Factor Surveillance System Questionnaire			•						•								
Smoking questionnaire			•						•								
Supplemental questions <sup>u</sup>			•						•								



	Screening	Confinement Period									Ambulatory Period						Safety Follow-up <sup>2</sup>
											Day 30 Visit ± 5 days		Day 60 Visit ± 5 days		Day 90 Visit ± 5 days		
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6 <sup>y</sup>	30	31	60	61	90	91	91 to 119
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
B: Bio-banking for BoExp and risk markers <sup>vw</sup>				•						•						•	
U: Bio-banking for BoExp and risk markers <sup>v</sup>				•					•						•		
B: Bio-banking for transcriptomics <sup>vw</sup>				•						•						•	
Nasal Epithelial collection <sup>x</sup>				•						•					•		
Buccal collection <sup>x</sup>				•						•					•		

Abbreviations: 8-epi-PGF<sub>2α</sub> = 8-epi-prostaglandine F<sub>2α</sub>; 11-DTX-B2 = 11-dehydro-thromboxane B2; AE = adverse event; Apo: Apolipoprotein; B = blood sample required; 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-C = high density lipoprotein cholesterol; HIV = human immunodeficiency virus; hs-CRP = highly sensitive C-reactive protein; HST = human smoking topography; LDL-C = low density lipoprotein cholesterol; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire of Smoking Urges; SA = smoking abstinence; SAE = serious adverse event; sICAM-1 = soluble inter-cellular adhesion molecule-1; THS = Tobacco Heating System; U = urine sample required; WBC = white blood cell count; TC = total cholesterol, TG = triglycerides.

a: Systolic and diastolic blood pressure, pulse rate, and respiratory rate (systolic and diastolic blood pressure were also analyzed as risk markers on Day 0, Day 6, Day 30 Visit [Day 30], Day 60 Visit [Day 60], and Day 90 Visit [Day 91]).

b: Including height (only at Screening). Weight was evaluated also as risk marker on Day -2 Visit on Day 90 Visit (Day 91).

c: Waist circumference was evaluated also as risk markers on Day -2 and Day 90 Visit (Day 91).

d: Spirometry without bronchodilator was performed at Screening only and was done prior to spirometry with bronchodilator.

Spirometry with bronchodilator was done at Screening, Day 0, Day 6, and Day 90 Visit (Day 91). At Screening, spirometry with bronchodilator was done at least 1 hour after smoking. On Day 0, Day 6, and Day 90 Visit, spirometry with bronchodilator was performed prior to product use (mCC or THS 2.2 Menthol).

Spirometry using helium technique and spirometry using the single breath technique for CO were performed on Day 0, Day 6, and Day 90 Visit (Day 91) prior to product use.





e: WBC count (leukocytes) and platelet count from the safety laboratory panel were 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 were evaluated 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) were permissible, if performed 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. On Day -1, the first test was conducted within 15 minutes prior to the first product use. On Day 5, the first test was conducted within 15 minutes prior to the first product use (for subjects in the THS Menthol 2.2 and mCC arms) and at between 08:00 AM and 09:30 AM for subjects in the SA arm. The other 3 tests were conducted as described in [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 done in conjunction with CO breath tests, where applicable.

Day -1 and from Day 1 to Day 4: one blood sample in the evening around 08:00 PM.

On Day 0, two blood samples were collected: one blood sample was collected prior to gas transfer assessment and prior to product use (the COHb levels measured served for adjustment of gas transfer values only), the second blood sample was collected in the evening between 08:00 PM and 09:30 PM.

Day 5: one blood sample within 15 minutes prior to first product use (for subjects in THS 2.2 Menthol and mCC arms) and between 08:00 AM and 09:30 AM for subjects in the SA arm. The 3 other blood samplings were be conducted as described in [Section 9.5.1.1.2](#).

On Day 6: one blood sample was collected prior to the gas transfer assessment and prior to product use (the COHb levels measured served for adjustment of gas transfer values only).

Day 30 Visit (Day 30), Day 60 Visit (Day 60): one blood sample was collected during the visit, irrespective of the time of product use.

On Day 90 Visit: one blood sample was collected on Day 90, irrespective of the time of product use. One blood sampling was collected on Day 91 prior to gas transfer assessment, and product use (the COHb levels measured served for adjustment of gas transfer values only).

j: Nicotine/cotinine; Day 0 to Day 4 (all study arms): one blood sample between 08:00 PM and 09:30 PM.

Day 5 and Day 6 (THS 2.2 Menthol and mCC arms): one sample within 15 minutes prior to the first product use; 8 blood samples after the start of product use ( $T_0$ ), each at 2-hour intervals. On Day 6, two blood samples were drawn. The first sample was 20 hours after  $T_0$  and the second blood sample was 24 hours after  $T_0$  (with  $T_0$  being the time of the first product use on Day 5).

Day 5 and Day 6 (SA arm): one blood sample in the evening between 08:00 PM and 09:30 PM on Day 5 and one blood sampling between 08:00 AM and 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 was 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 markers 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 markers on Day 0 and Day 90 Visit (Day 91).

n: Evaluated also as risk markers on Day 0, Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit.

o: Daily during Ambulatory Period only (from time of Discharge on Day 6 to time of Discharge of Day 91). Use of any tobacco/nicotine-containing products was 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-R; daily from Day 0 to Day 6 prior to product use, but no later than 10:00 AM and at every visit during the Ambulatory Period, i.e., Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91) no later than 10:00 AM irrespective of the time of product use.

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 the MCEQ was asked to all subjects, and from Day 1, MCEQ was asked to THS 2.2 Menthol and mCC arms only.

s: On Day 0, HST assessment was done in all subjects smoking mCC compatible with the HST SODIM<sup>®</sup> device. On Day 1, Day 4, Day 30 Visit (Day 30), and Day 60 Visit (Day 60), and Day 90 Visit (Day 90), HST was done in all subjects in the THS 2.2 Menthol and mCC arms. On Day 1 and Day 4, full day HST recording was done. On Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90), 4 hours of recording was done. Smoking topography with the HST SODIM<sup>®</sup> device was not done in subjects smoking mCC that were incompatible with the HST SODIM<sup>®</sup> device (e.g., slim mCC). No HST assessment was done in subjects in the SA arm.

t: Cough questionnaire was done daily from Day 0 to Day 6 prior product use but no later than 10:00 AM and on Day 30 Visit (Day 31), Day 60 Visit (Day 61), and Day 90 Visit (Day 91) no later than 10:00 AM, irrespective of product use.

u: Subjects were assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by the means of 2 questionnaires. The questionnaires were asked with the following sequence:

1-a standard questionnaire (Behavioral Risk Factor Surveillance System Questionnaire 2011 (31)) which was validated

2-an SQ which was validated. Immediately after the administration of the SQ, some supplemental questions were collected on the completion of the SQ questionnaire. This supplemental question 1 was related to the time which the subject spent to complete the SQ and was completed by site.

The Behavioral Risk Factor Surveillance System Questionnaire and the SQ were self-administrated to be answered by subjects. The supplemental questions were asked by the site.

v: Samples were only taken if additional consent for bio-banking was given by the subject.

w: Following at least 10 hours of fasting condition.

x: Subject has not eaten within 30 minutes prior to the start of procedures.

y: All examinations listed at the Day of Discharge (Day 6) were conducted in subjects whose participation in the study was prematurely terminated and for all subjects who had tried the product on Admission.

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

**Table 9 Schedule for 4-hour Urine Collection Assessments**

	Baseline Period 4-hour urine fraction	Ambulatory Period 4-hour urine fraction
	Day 1	Day 90 Visit (Day 91)
BoExp in urine <sup>a</sup>	•	•
Creatinine	•	•
11-DTX-B2, 8-epi-PGF <sub>2α</sub>	•	

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

Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; 8-epi-PGF<sub>2α</sub> = 8-epi-prostaglandine F<sub>2α</sub>; 11-DTX-B2 = 11-dehydro-thromboxane B2; BoExp = biomarker(s) of exposure; CEMA = 2-cyanoethylmercapturic acid; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; MHBMA = monohydroxybutenyl mercapturic acid; NEQ = nicotine equivalents; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid; Total NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; Total NNN = N-nitrosonornicotine.


**Table 10 Schedule for 24-hour Urine Collection Assessments**

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

a: MHBMA, 3-HPMA, S-PMA, Total NNAL, 1-OHP, 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 the relevant sample bio-banking was given by the subject.

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





### 9.5.8 Appropriateness of Measurements

The laboratory measures utilized 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/abstinence;
- timeframe of reversibility of measure in the perspective of the study duration;
- practicality/acceptability by subjects; and
- robustness of the method (rapid, simple, accurate).

All questionnaires utilized for this study (except the cough, socio-economic, smoking, and HST questionnaires) were available as validated questionnaires.

## 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 CRO Clinical Research Associate (CRA) was responsible for the monitoring of the study. Monitoring was performed according to the CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

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

The Principal Investigator accessed medical records for the Monitor in order that entries in the CRFs could be verified. The Principal Investigator, 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 was held in Daytona Beach, Florida on 05 December 2013 prior to the Site Initiation Visit (SIV). During this meeting, the general training of the 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

Following delivery of the IP demonstration device, SIVs of approximately 8 hours were conducted at the sites by Monitors after the Investigator's meeting. Activities of the SIVs are described in detail in the protocol ([Appendix 16.1.1](#)).



Once the SIVs were completed and once IP and Clinical Supplies were received at site and properly inventoried and stored and all applicable approvals were gained, the site was eligible to screen and randomize subjects.

#### 9.6.1.3 Routine Monitoring Visits

Communication by telephone, mail, and e-mail was 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 site staff, was available during the monitoring visit to review the data and resolve any queries, and to allow direct access to the subject's records for source data verification.

#### 9.6.1.4 Close Out Visit

Visits were conducted according to Covance's SOP CO-SOP-005 'Preparing for, Conducting and Reporting Close Out Visits (COVs)' and the PMP COV Report template was used. The Philip Morris Clinical Study Manager informed Study Lead CRA and Monitors when the COV was to be conducted. The COV occurred within 2 weeks of notification from the Sponsor. The Monitor was responsible for performing the COV after all CRFs were completed, sent to Covance Data Management, all data clarification forms were resolved, and the database was locked.

The purpose of the COV included:

- Ensuring that all CRF pages were monitored by Monitors and frozen by the Data Management team.
- Performance of final IP accountability (if not already completed), ensuring the return (or destruction) of remaining IP and IP supplies, and checking that all returns were properly documented.
- Final checking to ensure all laboratory samples had been shipped from the site.



- Final checking that all e-diaries, devices, HST SODIM<sup>®</sup> devices, and butt/filter collectors were shipped back and lab kits destroyed, and checking that all returns had been properly documented.
- Reviewing completion and accuracy of the Study Site File (SSF) as per the SSF checklist, including Monitoring Visit Log, Site Responsibility Log, Subject Screening and Enrollment Log, IP shipment & accountability logs, and all applicable logs and documents.
- Reviewing the procedure for record retention, Independent Ethics Committee (IEC)/IRB notification, and publication rights with the Principal Investigator.
- Advising site to notify the IEC/IRB of study closure.

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,
- Presentation of reporting of protocol deviations,
- Presentation of IP and devices,
- Training on HST and use of HST SODIM<sup>®</sup> device,
- Laboratory Sample Handling Manual - kits and labels - laboratory shipments, laboratory documentations,
- Presentation of safety reporting procedures - AE and SAE forms and SAE handling,
- Pregnancy reporting procedures - pregnancy form and pregnancy handling,
- Refreshment training on GCP requirements,
- (b) randomization procedure and training,
- Electronic data capture system training,
- Presentation of query process,
- ePRO training,
- Presentation on lung function assessments,
- Presentation on monitoring requirements.

Site staff received initial training at the Investigator meeting. Site staff members not initially trained at the meeting were trained by the monitor during the SIV and, if required, training was provided on an ongoing basis throughout the study.

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





### 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 (DMP) and documents specified therein.

#### 9.6.3.1 Data Capture

With the exception of subject reported outcome data, all results from the clinical assessments were recorded in the source documents by the Principal Investigator or their 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 Investigator had ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data were accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF was electronically signed by the Principal Investigator to attest that the data contained in the CRF were true and accurate. Any corrections made to source documents and/or CRFs were clearly recorded, without obscuring the original values and were accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject was checked against the source documents at the study site by the Monitor. Instances of missing or unclear data were discussed with the Principal Investigator for resolution. For the ePRO diary, all subject reported outcome data was provided in English and instructions were provided in the subject's local language. A CRF was generated for all subjects that signed informed consent.

A copy of the CRF, the subject questionnaires, 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 the Clinical Trial Management System or other approved format. The protocol deviation categorization was entered by the Sponsor. Further details on the recording of protocol deviations are provided in the protocol ([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





DMP, reviewed and approved by the Sponsor. 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 Handling

The data were validated as defined in the DMP and Data Validation Specifications. Discrepancies were generated electronically as necessary.

Data queries were raised for discrepant or missing data and 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:

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

THS 2.2 Menthol device issues and malfunction were classified according to C54451/Medical Device Problem Codes, FDA, Center for Devices and Radiological Health (34).

#### 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.



After data review by the Sponsor, resolution of all raised queries and QC of the changed data, the database or selected data upon Sponsor approval as applicable was/were declared locked.

Any changes to the database after that time could only be made by written agreement between the Sponsor and the Data Management and Statistical Team at Covance. Any such changes were formally documented.

After study completion, the study database was transferred to the Sponsor in the format specified in the DMP in Clinical Data Interchange Standards Consortium Study Data Tabulation Model Data Structure Specifications.

#### 9.6.4 Audits and Inspections

Good Clinical Practice regulations required that there were independent inspections of clinical program activities. Such inspections could have been 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 or designee contacted the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.

The Principal Investigator and study site staff were responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that was suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the Principal Investigator or designee 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

The statistical evaluation was performed using Statistical Analysis Software® (SAS®), Version 9.3.

#### 9.7.1.2 Data Sets for Analysis

The per protocol (PP) set 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 11](#)).

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

Safety was analyzed using the Safety Population by randomization arm and according to product use categories (see [Table 11](#)).

##### 9.7.1.2.1 Full Analysis Set

The FAS consisted of all randomized subjects who had at least one post-randomization product use experience, if randomized to THS 2.2 Menthol or mCC, and had at least one valid non-safety assessment (THS 2.2 Menthol, mCC, and SA arms).

##### 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 of the study's primary objectives (as defined in Section 11.1.1 of the SAP [[Appendix 16.1.8](#)]).

The PP Set was assessed for each product use time period 1 to 4 (see [Table 11](#)), considering the product deviations occurring only during that period, independent of any exclusion from the population in previous periods.

**Table 11 Stratification Labels for Product Use**

Stratification Factor	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%]
PP Set 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 ([5 - 30]%) Primarily CC ([0 - 5]%) Exclusively CC (0%)

#### 9.7.1.2.3 Safety Populations

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

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

#### 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, subjects from the mCC arm who were exclusive users of mCC, or for subjects in the SA arm who were abstinent, as defined in Section 6.3.3.2 of the SAP ([Appendix 16.1.8](#)).





### 9.7.1.3 Stratification

Each sex and each of the current mCC consumption levels (10 to 19 mCC/day and >19 mCC/day) had a quota applied to ensure that 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 summarized for the Safety Population, FAS, and the PP Set in Periods 1-4.

The demographic variables age, sex, race, body weight, height, BMI, and waist circumference were listed and summarized by randomization arm, and by the 2 stratification factors (sex and mCC consumption) using the following descriptive statistics: number of subjects, number and percent of subjects with missing data, arithmetic mean, arithmetic standard deviation (SD), 95% confidence interval (CI), median, first and third quartiles, minimum and maximum, and number and/or counts and percentages within specific categories.

Other baseline characteristics were also included in the table. No inferential analyses were presented 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 number of mCCs smoked (categorized as 10 to 19 cigarettes/day and >19 cigarettes/day) was summarized and listed at Admission (Day -2). 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 mCC 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 of the SES categories were summarized with baseline characteristics data 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 staff 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 for the FAS.

During the Ambulatory Period, subjects in the 3 study arms captured (from the time of Discharge on Day 6 to Day 90) the number of products used (e.g., menthol and non-menthol CCs, 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 served as a compliance tool in all 3 arms. On Day 6/Discharge Confinement, the compliance to the product was ensured using both the accountability log (from 06:30 AM to time of Discharge) and the product use electronic diary (filled from the time of Discharge on Day 6 to Day 90).

#### 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 were summarized over the whole Ambulatory Period, as recorded by the subject, and for Periods 2 to 4.

All summaries were produced for the Safety Population, and for the PP Set for Periods 1 to 4. Summaries of data in the Ambulatory Period were also repeated for the FAS, if the population differed from the Safety Population by more than 10%. In addition, the number and percentage of subjects falling into each product use category ([Section 9.4.12.1](#)) during the Ambulatory Period was presented. The average product use data was also presented by randomized product and by product use category ([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
- Alcohol breath test
- Prior medication
- Willingness to use THS 2.2 Menthol products
- Product preference question

Prior and concomitant medications were listed by product using preferred term (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 summarized by randomization arm for the Safety Population, showing the number and percent of subjects who used the medication at least once by ATC 1st and 2nd levels and PT.

Product preference was collected at Admission (Day -2) and stated the product which the subject preferred to be randomized to (THS 2.2 Menthol, mCC, SA, or NP). Data were summarized by randomization arm along with baseline characteristics. Willingness and ability to use the product were 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 Endpoints

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

The BoExp used for the primary analysis were summarized using descriptive statistics including the number of subjects, number and percent of subjects with missing data, arithmetic mean, arithmetic SD, 95% CI, median, first and third quartiles, and minimum and maximum; for log-normal data the geometric mean, geometric 95% CI, and geometric coefficient of variation (CV) were also presented.

The primary endpoints were log-transformed (base<sub>e</sub>) prior to analysis. The analysis compared the evening COHb level (20:00 PM to 21:30 PM) on Day 5; urinary concentrations of MHBMA, 3-HPMA, and S-PMA adjusted for creatinine on Day 5; and urinary concentrations of Total NNAL adjusted for creatinine at the Day 90 Visit between





the THS 2.2 Menthol and mCC arms for the PP Set. An analysis of covariance (ANCOVA) (35) 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), and randomization arm.

The least squares (LS) means, 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 presented in the tables. In addition, THS 2.2 Menthol : mCC effects were graphed in a forest plot.

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

The hypothesis tested for each primary BoExp analysis endpoint 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 Day 90 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 for Day 5 and Day 90 data by means of a mixed model approach, without the last observation carried forwards data imputation described in [Section 12.1.5](#) of the SAP ([Appendix 16.1.8](#)). Any data outside of the allowed time window (see [Table 23](#) of the SAP [[Appendix 16.1.8](#)]) on Days 5 and 90 were 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 were repeated 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 analysis of COHb, MHBMA, 3-HPMA, and S-PMA on Day 90 and Total NNAL on Day 5 were performed for the PP Set.

The analysis 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 concentration 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; and the subject's last assessment prior to 10:00 AM on Day 1 in the SA arm.

#### 9.7.1.6.1 Analysis of Biomarkers of Exposure for Secondary Endpoints

The BoExp for the secondary endpoints 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, Total NNAL and NEQ (all analyzed from a 24-hour urine collection) on Day 5 and Day 90 were described as reported in [Section 9.7.1.5.1](#). Urine parameters were analyzed as concentrations 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 presented as above.

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

BoExp were analyzed using the same model described in [Section 9.7.1.5.1](#). No adjustments were made for multiple comparisons. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value  $\leq 0.025$ ) 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 presented in the tables (for exhaled CO, the difference in LS means and 95% CI were presented). Forest plots of the ratios and 95% CIs were also produced.

BoExp 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](#) "Sensitivity Analysis" for the BoExp for primary objectives was 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, sex, average daily mCC consumption over the last 4 weeks as reported during Screening, and product. 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 presented in the tables.



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

#### 9.7.1.6.3 Nicotine and Cotinine Pharmacokinetic Parameters

The peak nicotine and cotinine plasma concentration ( $C_{\text{peak}}$ ) and  $t_{\text{peak}}$  were obtained directly from the concentrations taken on Day 5. If the peak concentration occurred at more than one time point then  $t_{\text{peak}}$  was assigned to the first value. The weighted average concentration over 24 hours ( $C_{\text{avg}}$ ) on Day 5 was calculated by dividing the area under the curve from 0 to 24 h ( $\text{AUC}_{0-24 \text{ h}}$ ) by 24, where the  $\text{AUC}_{0-24 \text{ h}}$  was calculated using the linear trapezoidal rule. The data were listed and summarized for both nicotine and cotinine.

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  $C_{\text{peak}}$  (and  $t_{\text{peak}}$ ) could have occurred at any time.

The analysis compared the log-transformed  $C_{\text{peak}}$  and  $C_{\text{avg}}$  on Day 5 between the THS 2.2 Menthol and mCC arms. An analysis of variance model was used with terms for sex, average daily mCC consumption over the last 4 weeks as reported during Screening, and randomization arm.

Least squares means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were presented in the tables.

For  $t_{\text{peak}}$  on Day 5, the comparison between the THS 2.2 Menthol and mCC arms was made by the Wilcoxon Rank Sum test using PROC NPAR1WAY in SAS. Median difference and 95% CI using the Hodges-Lehmann estimate were tabulated.

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

#### 9.7.1.6.4 CYP1A2 Activity

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

The 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 activity was measured in plasma on Day 0, Day 5, and Day 90. Descriptive statistics of the values and percent change on Days 5 and 90 from Day 0, 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, sex, average daily mCC consumption over the last 4 weeks as reported during Screening, and randomization arm. No adjustments were made for multiple comparisons. If the results from the Day 5 analysis were significant (one-sided p-value  $\leq 0.025$ ) then the statistical significance was to be 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 presented in the tables.

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 of the use of a concomitant medication which affects CYP1A2 activity, the analysis was repeated by excluding these assessments for both the PP Set and FAS. All summaries and analyses were performed on 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 Day 90 between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms for the FAS and PP Set. An ANCOVA model was used with terms for baseline, sex, average daily mCC consumption over the last 4 weeks as reported during Screening, and randomization arm. No adjustment was made for multiple comparisons.

Blood pressure, HbA1c, LDL-C, HDL-C, TG, TC, WBC (leukocytes), body weight and waist circumference were analyzed in the regular scale. 8-epi-PGF<sub>2α</sub>, 11-DTX-B2, and sICAM-1 were analyzed in the logarithmic scale. Other CREs were logarithmically transformed prior to analysis if there was evidence of non-normality by means of Shapiro-Wilks test.





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 presented in the tables along with a forest plot of the results.

If there were any 11-DTX-B2 assessments performed within 5 half-lives of the use of a concomitant medication which affects production of 11-DTX-B2, the analysis was repeated excluding these assessments for both the PP Set and FAS. All tables, figures, and analyses were produced for the FAS and PP Set. Forest plots were only produced for the PP Set.

#### 9.7.1.7 Exploratory Analysis

##### 9.7.1.7.1 Biomarkers of Exposure in 4-hour Fraction

The BoExp MHBMA, 3-HPMA, S-PMA, Total NNAL, 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 4-hour fraction) on Day -1 and Day 91/Discharge Ambulatory were described as reported in [Section 9.7.1.5.1](#). The parameters were analyzed as concentrations adjusted for creatinine. All BoExp were analyzed in the log scale.

BoExp on Day 90 were analyzed using the same model described in [Section 9.7.1.5.1](#). No adjustment was made for multiple comparisons.

Least squares means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were presented in the tables.

BoExp were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as above for the PP Set.

All summaries and analyses were performed on the PP Set.

##### 9.7.1.7.2 Questionnaires

###### Fagerström Test for Nicotine Dependence Questionnaire

The FTND in its revised version ([24](#)) was conducted at Screening to determine subject's dependence on nicotine and on the Day 90 Visit to assess any changes in their dependence on nicotine.

[Table 12](#) shows the 6 questions and the scores associated with each question.



**Table 12 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 prohibited?	• Yes	1
	• No	0
3. Which cigarette would you hate most to give up?	• The first one in the morning	1
	• Any other one	0
4. How many cigarettes per 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 even if you are so sick 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 if all items were non-missing (otherwise the total score were set to missing).

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

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

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

All summaries and shift tables were performed on the PP, FAS, and Compliant Population.

*Questionnaire of Smoking Urges-Brief*

Details of the QSU-brief (27) are presented in [Section 9.5.6.4.4](#). The QSU-brief consists of 10 items as presented in [Table 13](#).

**Table 13 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 indicated a higher urge-to-smoke.

Two factor scores and a total score were derived (27). Each factor was a subset that includes 5 of the 10 questions as defined in [Table 13](#). 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 domain scores (relief and reward). The total score and 2 domain scores, along with the percent change from baseline were summarized. The answers to the individual questions, along with the domain 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 domain scores were produced.

The analysis was performed separately for each post-baseline time point in the domain and total scores. An ANCOVA model was used with terms for baseline QSU-brief score, sex, average daily mCC consumption over the last 4 weeks as reported during Screening, and randomization arm. No adjustment 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% CIs were presented in the tables.

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

#### Modified Cigarette Evaluation Questionnaire

Details of the MCEQ (26) are presented in [Section 9.5.6.4.3](#). The MCEQ consisted of 12 items as presented in [Table 14](#).

**Table 14 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 indicated 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 analyses were presented for the THS 2.2 Menthol and mCC only. The MCEQ was not captured for the SA arm.

The domain scores, along with the percent change from baseline, were summarized. The answers to the individual questions, along with the domain 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, sex, average daily mCC consumption over the last 4 weeks as reported during Screening, 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 presented in the tables.

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

#### Minnesota Nicotine Withdrawal Questionnaire

The MNWS-R (29) is a 24-hour recall that was completed by the subject daily from Day 0 to Day 6/Discharge Confinement, and on the second day of every visit during the Ambulatory Period. From Day 0 to Day 6/Discharge Confinement only, MNWS-R questionnaires were 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-R was conducted irrespective of the time of product use but no later than 10:00 AM, and on Day 91/Discharge Ambulatory the assessment of MNWS-R was conducted prior to smoking but no later than 10:00 AM.

The self-reported part of the MNWS-R consisted of the following 15 items in Table 15 which were rated over the last 24 hours on a scale of 0 to 4.



**Table 15 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

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.

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

The total score, along with the percent change from baseline, was summarized. The answers to the individual questions, along with the total score, and the changes and percent changes 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, sex, and average daily mCC consumption over the last 4 weeks as reported during Screening. 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 presented in the tables.

All figures, summaries, and analyses were performed on 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<sup>®</sup> device (i.e., non-slim mCC), and on Day 4, Day 30, Day 60, and Day 90 for all subjects in the THS 2.2 Menthol and mCC arms (except mCC which were not compatible with the HST SODIM<sup>®</sup> 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 CC/products is different with the device.
2. You enjoy smoking with the device as much as without it.
3. The taste of the CC/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 were summarized. The individual responses were listed.

All summaries were performed on the PP Set.

### Behavioral Risk Factor Surveillance System Questionnaire

Subjects were assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by a standard questionnaire (Behavioral Risk Factor Surveillance System Questionnaire 2011 (31) which was validated.

The Behavioral Risk Factor Surveillance was self-administrated, to be answered by subjects. The standard questionnaire consists of 5 questions. All 5 questions are close-ended questions and the responses are exhaustive and mutually exclusive. The questions are shown in [Table 16](#).

**Table 16 Behavioral Risk Factor Surveillance System Questionnaire**

Question	Response
1 Have you smoked at least 100 cigarettes in your entire life?	Yes No Don't know/Not sure Refused
2 Do you now smoke cigarettes every day, some days or not at all?	Every day Some days Not at all Don't know/Not sure Refused
3 During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking?	Yes No Don't know/Not sure Refused
4 How long has it been since you last smoked a cigarette, even one or two puffs?	Less than 1 month ago 1 month but less than 3 months ago 3 months but less than 6 months ago 6 months but less than 1 year ago 1 year but less than 5 years ago 5 years but less than 10 years ago 10 years or more Don't know/Not sure Refused
5 Do you currently use chewing tobacco, snuff, or snus every day, some days, or not at all	Every day Some days Not at all Don't know/Not sure Refused

The individual responses were listed only.

#### Smoking Questionnaire

Subjects were assessed for their current and past smoking behavior at baseline on Day -1 and on Day 5 by an SQ which was validated by the supplemental questions.

The SQ was self-administrated, to be answered by subjects. The SQ focused on self-reported current and past cigarette smoking behavior. The SQ consisted of 8 questions. The first 3 questions are close-ended questions and the responses are exhaustive and mutually exclusive. The last 5 questions refer to the individual smoking history and are answered to the degree applicable. The SQ questions are shown in [Table 17](#).

**Table 17 Smoking Questionnaire**

Question	Response
1 What is your current cigarette smoking behavior (including hand-rolled cigarettes)?	Daily smoker (at least one cigarette per day, disregarding religious fasting) Occasional smoker (less than one cigarette per day) Ex-smoker of cigarettes Non-smoker of cigarettes
2 Have you smoked at least 100 cigarettes in your entire life?	Yes No
3 Did you ever smoke cigarettes regularly, i.e., at least 1 cigarette per day?	Yes No
4 If you ever smoked cigarettes regularly: At what age did you start to smoke regularly?	Age in years
5 If you are an ex-smoker of cigarettes: For how long have you quit now?	Time in years, months, and days
6 If you ever quit regular cigarette smoking: For how long did you quit altogether?	Time in years, months, and days
7 What brand of cigarettes/hand-rolled tobacco did you predominantly smoke in the last 12 months of smoking?	Open question
8 On average, how many cigarettes/cigars/pipes do/did you smoke per day currently / 1 year ago / 5 years ago / 10 years ago / 15 years ago / 20 years ago / More than 20 years ago?	For each category and time point: None Less than 1 per day Actual number

The daily CC consumption reported in these questionnaires was not used for eligibility.

The supplemental questions consisted of 8 questions which were asked by the site. The data from these questionnaires were described as part of the CSR, but the analysis of this data to validate the SQ is the subject of a separate report. The supplemental questions are shown in [Table 18](#).



**Table 18 Supplemental Questions from Smoking Questionnaire**

Question	Response
1 How long did it take for the subject to complete the SQ?	Answer in minutes
2 Did the SQ capture your smoking behavior completely?	Yes No
3 Did the SQ capture your smoking behavior correctly?	Yes No
4 Did the SQ capture your smoking history completely?	Yes No
5 Did the SQ capture your smoking history correctly?	Yes No
6 Was the SQ self explaining?	Yes No
7 Was the SQ easy to use?	Yes No
8 Any comments	Open-ended question

The individual responses were listed only.

*Prochaska 'Stage of Change' Questionnaire: Intention to Quit Smoking*

The Prochaska 'Stage of Change' questionnaire was used to assess the smokers' mental state for the intention to quit (See Appendix 5 of the protocol for staging algorithm [Appendix 16.1.1]).

The Prochaska 'Stage of Change' questionnaire was performed at Screening, Day -2, Day 30, Day 60, and Day 90. On Day -2 the Prochaska 'Stage of Change' questionnaire was asked to the subject prior to product trial. The questions are shown in Table 19.

**Table 19 Prochaska 'Stage of Change' Questionnaire**

Question	Response
1 Are you currently a smoker?	Yes No: quit in last 6 months No: quit more than 6 months
2 In the last year, how many times have you quit smoking for at least 24 hours	Number of times
3 Are you seriously thinking of quitting smoking?	A) Yes, within the next 30 days B) Yes, within the next 6 months C) No, not thinking of quitting

The Prochaska 'Stage of Change' Questionnaire results were summarized on the FAS and Compliant Population, and individual responses were listed.

#### 9.7.1.7.3 Human Smoking Topography Assessment

The HST assessments took place on Day 0, Day 1, Day 4, Day 30, Day 60, and Day 90 in the THS 2.2 Menthol and mCC arms only, if mCC were compatible with the HST SODIM<sup>®</sup> device. On Day 0, Day 1, and Day 4 the HST was conducted on each product use. On Day 30, Day 60, and Day 90 the HST was recorded over a 4-hour period only.

The HST SODIM<sup>®</sup> device measured and recorded the flow and other per-puff parameters listed in [Table 20](#).

**Table 20 Human Smoking Topography – Per-Puff Parameters**

Description	Variable	Unit
Puff number	$N_i$	puff
Puff volume	$V_i$	mL
Puff duration	$D_i$	s
Average flow [ $V_i/D_i$ ]	$Q_{mi}$	mL/s
Peak flow	$Q_{ci}$	mL/s
Inter-puff interval	$I_i$	s
Sum of $I_i$ and $D_i$	$D_{Fi}$	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



From the per-puff parameters, the per-cigarette parameters shown in [Table 21](#) were derived (representing average values or totals per cigarette).

**Table 21 Human Smoking Topography – Per-Cigarette Parameters**

Description	Variable	Formula	Unit
Total number of puffs	NPC	$\sum N_i$	puff
Total puff volume	TVOL	$\sum V_i$	mL
Average puff volume	AvgV <sub>i</sub>	$\sum V_i / NPC, i=1 \dots NPC$	mL
Average puff duration	AvgD <sub>i</sub>	$\sum D_i / NPC, i=1 \dots NPC$	s
Total puff duration	TD <sub>i</sub>	$\sum D_i$	s
Average flow	AvgQ <sub>mi</sub>	$\sum Q_{mi} / NPC, i=1 \dots NPC$	mL/s
Average peak flow	AvgQ <sub>ci</sub>	$\sum Q_{ci} / NPC, i=1 \dots NPC$	mL/s
Total inter puff interval	TI <sub>i</sub>	$\sum I_i$	s
Average inter puff interval	AvgI <sub>i</sub>	$\sum I_i / NPC, i=1 \dots NPC$	s
Total smoking duration	TDF <sub>i</sub>	$\sum DF_i$	s
Total work	TW <sub>i</sub>	$\sum W_i$	mJ
Average work	AvgW <sub>i</sub>	$\sum W_i / NPC, i=1 \dots NPC$	mJ
Average pressure drop	AvgP <sub>mi</sub>	$\sum P_{mi} / NPC, i=1 \dots NPC$	mmWg
Average peak pressure drop	AvgP <sub>ci</sub>	$\sum P_{ci} / NPC, i=1 \dots NPC$	mmWg
Smoking intensity	SMINT	TVOL/TDF <sub>i</sub>	mL/s
Puffing time Index	PTI	$(100 \cdot TD_i) / TDF_i$	%
Puff frequency	PF <sub>eq</sub>	$NPC / (TDF_i / 60)$	puffs/min

Prior to calculation of the per-cigarette parameters, the topography data was processed through analysis software. Only data that were declared “accepted” by the software contributed to the per-cigarette parameters and were part of the study database.

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 averaged over the visit were presented graphically.

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

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

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



#### 9.7.1.7.4 CYP2A6 Activity

Cytochrome P450 2A6 activity was calculated in plasma as the metabolic ratio of *trans*-3' hydroxycotinine and cotinine, both expressed in molar equivalent (nmol/L) (23).

The conversion factor was applied as follows:

Cotinine	The molecular weight is 176.215 g/mol. Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL was multiplied by 5.675.
<i>Trans</i> - 3'hydroxycotinine	The molecular weight is 192.217 g/mol. Therefore to transform <i>trans</i> -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/Discharge Confinement and Day 91/Discharge Ambulatory. Descriptive statistics of the values and changes on Day 6/Discharge Confinement and Day 91/Discharge Ambulatory from Day 0 and supportive listings were provided.

If either of the cotinine or *trans*-3'hydroxycotinine concentrations were less than the lower limit of quantification then the ratio was not calculated.

The analysis compared the log-transformed Day 6/Discharge Confinement 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, sex, and average daily mCC consumption over the last 4 weeks as reported during Screening, and randomization arm. No adjustment was made for multiple comparisons. If the results from the Day 6/Discharge Confinement analysis were significant (one-sided p-value  $\leq 0.025$ ) then the statistical significance was repeated for the analysis on the Day 91/Discharge Ambulatory values.

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

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

If there were any CYP2A6 assessments performed within 5 half-lives of 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 on the FAS and PP Set.





#### 9.7.1.7.5 Relationship Between Biomarkers of Exposure and Nicotine Equivalents

The analysis of the relationship between NEQ and primary and secondary BoExp were reported in a separate report.

#### 9.7.1.7.6 Relationship Between Risk Markers and Biomarkers of Exposure and Nicotine Equivalents

The analysis of the relationship between CREs, primary and secondary BoExp, and NEQ were reported in a separate report.

#### 9.7.1.7.7 Ames Mutagenicity Test

The 24-hour urine collections for the Ames mutagenicity test were performed on Day 0, Day 5, and Day 90.

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

All summaries were performed on the FAS and PP Set.

#### 9.7.1.7.8 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 paper", and "Missing".

All summaries were performed on the FAS only.

#### 9.7.1.7.9 Oxysterols

Plasma concentrations of 6 $\alpha$ -hydroxy-5 $\alpha$ -cholestane, 7 $\alpha$ -hydroxycholesterol, 5 $\alpha$ ,6 $\alpha$ -epoxycholestanol, 7-ketocholesterol, 7 $\beta$ -hydroxycholesterol, 5 $\beta$ ,6 $\beta$ -epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, TC, 22(R)-hydroxycholesterol, and 4 $\beta$ -hydroxycholesterol were measured in plasma on Day 0, Day 6/Discharge Confinement, and Day 91/Discharge Ambulatory.

Descriptive statistics of the values and changes on Day 6/Discharge Confinement and Day 91/Discharge Ambulatory from Day 0 and supportive listings were provided.

All summaries and figures were performed on the FAS and PP Set.



#### 9.7.1.7.10 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 presented categorized separately by product preference and by product use categorization (see [Section 9.4.12.1](#)).

#### 9.7.1.7.11 Concordance Between 24-hour Urine Collection and 4-hour Urine Fraction

The concordance was investigated between MHBMA, 3-HPMA, S-PMA, Total NNAL, Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ, 8-epi-PGF<sub>2α</sub>, and 11-DTX-B2 (expressed as concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at baseline and on the Day 90 Visit.

Concordance was also investigated between MHBMA, 3-HPMA, S-PMA, Total NNAL, Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ, 8-epi-PGF<sub>2α</sub>, and 11-DTX-B2 (expressed as change in concentration adjusted for creatinine in 24-hour urine collection and change in concentration adjusted for creatinine in 4-hour urine fraction from baseline to Day 90 Visit).

Scatterplots between each pair of variables were produced showing the Spearman Rank correlation coefficient on the plot. In addition, Bland-Altman (36) plots of the data were produced including the mean of the differences and the 95% CI. In these scatterplots the data from the 24-hour urine collection were on the x-axis. These were produced for the FAS and presented in an Appendix of the CSR.

#### 9.7.1.7.12 Biomarkers of Exposure in Subjects Quitting Smoking

The data to be followed for subjects who quit smoking were:

Carbon monoxide (ppm) in exhaled breath, COHb in blood (%), urinary BoExp and NEQ (expressed as quantity excreted and concentration adjusted for creatinine) in both 24-hour urine collection and 4-hour fraction, hs-CRP, homocysteine, blood glucose, LDL-C, HDL-C, TG, TC, fibrinogen, HbA1c, sICAM-1, total WBC (leukocytes) count, platelet count, 8-epi-PGF<sub>2α</sub>, and 11-DTX-B2.

These data were plotted and summarized versus time since quitting for all subjects who quit smoking. The time since quitting was rounded up to the nearest 30 days, such that a subject who quit before the Day 30 Visit was assumed to have quit smoking for 30 days at the Day 30 Visit, 60 days at the Day 60 Visit, and 90 days at the Day 90 Visit.



Similarly, a subject who quit smoking between the Day 30 Visit and the Day 60 Visit was assumed to have quit smoking for 30 days at the Day 60 Visit and 60 days at the Day 90 Visit, and a subject who quit smoking between the Day 60 Visit and the Day 90 Visit was assumed to have quit smoking for 30 days at the Day 90 Visit.

The data were to be presented in a separate Appendix of the CSR if more than 5 subjects in the FAS quit smoking in the THS 2.2 Menthol or mCC arms.

## 9.7.2 Post-hoc Analyses

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

### 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 was 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 one AE were produced by randomization arm for the pre-randomization and randomized periods; AE data during the randomized period were also presented stratified by Confinement, Ambulatory, and Safety Follow-up.

Ambulatory AE data were also reported by product use category (see [Table 11](#)), defined on product use over the whole Ambulatory Period. In particular, the general product use categories for THS 2.2 Menthol were used, and the [Predominantly Abstinence] and [Smoking Abstinence] categories were presented for THS 2.2 Menthol and mCC arms if at least one subject was associated to these categories.



#### 9.7.3.1.1 All Adverse Events

A general summary table of AEs was presented including:

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

Additional summary tables of AEs were presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by system organ class (SOC) and PT coded according to the MedDRA dictionary (Version 16.0).

If a subject had more than one 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 the AE was counted as severe.

#### 9.7.3.1.2 Serious Adverse Events (Including Deaths)

A summary table of SAEs was presented 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 one 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 presented for AEs leading to discontinuation, by product as described in [Section 9.7.3.1](#).

AEs leading to discontinuation 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.

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 1st and 2nd levels and preferred drug name.

### 9.7.3.3 Laboratory Safety Parameters

[Table 6](#) lists the hematology, clinical chemistry, and urinalysis parameters to be 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 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 worsened 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 Exposure Period were presented in tables 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 clinically significant (CS) results (as defined by Principal Investigator comment), and CTCAE toxicity grading were tabulated for laboratory



parameters, together with shift in normality (Normal, Abnormal not CS [NCS], Abnormal CS) 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 CS (as defined by the Principal Investigator comments) and shift from baseline, the Principal Investigator comments, the CTCAE grade and the shift in CTCAE grade. Only CTCAE grades greater than zero were presented.

#### 9.7.3.4 Physical Examination

Physical examination data recorded at the Screening Visit, Admission (Day -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 CS physical examination findings were flagged. The number of subjects (%) with normal, abnormal, and abnormal CS 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 and waist circumference (recorded at Admission [Day -2], Day of Discharge [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 Admission and Day of Discharge were presented for the Safety Population.

The BMI was also categorized into underweight ( $<18.5 \text{ kg/m}^2$ ), normal range ( $\geq 18.5$  and  $<25.0 \text{ kg/m}^2$ ), overweight ( $\geq 25.0$  and  $<30.0 \text{ kg/m}^2$ ), 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 presented for supine systolic and supine diastolic blood pressure, pulse rate, and respiratory rate at baseline, and on every subsequent day of both the Confinement and Ambulatory Periods by product for each study day. Vital signs data 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/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90



Visit) together with changes from baseline and shifts in normality. Electrocardiogram data from subjects who had significant clinical findings were highlighted in listings.

Descriptive statistics were presented for ECG data at baseline, and Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit by randomization arm. ECG data were summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal CS results.

#### 9.7.3.7 Full Lung Function Data

Lung function parameters assessed during the study included:

- DLCO
- KCO
- FEV<sub>1</sub>
- FVC
- VC expressed as L
- TLC
- FRV
- IC
- MEF 25-75
- Measurement interpretation (categories: normal, abnormal, abnormal CS)

The above data were collected at Screening, Day 0, Day of Discharge (Day 6), and Day 90 Visit. At Screening, data were collected prior to and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator. All other spirometry assessments were performed with bronchodilator.

Spirometry predicted values were standardized to the National Health and Nutrition Examination Survey III predicted set (37). Spirometry data values and normality evaluation were listed by randomization arm and study day. Assessments performed after baseline were listed together with change from baseline and shift in normality. Spirometry data from subjects who had significant clinical findings were highlighted in listings.

Descriptive statistics were presented for DLCO, KCO, FEV<sub>1</sub>(L), FEV<sub>1</sub> (% pred), FVC(L), FVC(% pred), FEV<sub>1</sub>/FVC, VC, TLC, FRV, IC, MEF 25-75 at baseline (prior to or without bronchodilator), Day of Discharge (Day 6), and Day 90 Visit by randomization 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 NCS/abnormal CS 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 was defined as any condition that was ongoing at Screening. Medical history and concomitant disease were coded using MedDRA (Version 16.0) and listed separately by randomization arm, SOC, and PT within SOC.

Medical history and concomitant disease were summarized by randomization arm, SOC, and PT for the Safety Population.

### 9.7.3.9 Assessment of Cough

Details of the cough assessments and timings of assessments are provided in [Section 9.5.6.4.2](#).

The number and percentage of subjects reporting a cough were summarized by randomization arm and presented for the day prior to the assessment. The responses to the individual items, including the VAS evaluating the level of cough bother and the 3 Likert scales measuring the intensity and 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 relating to any other important observations 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 PMI controlled terminology.

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

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

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





### 9.7.3.11 Product Compliance

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

### 9.7.3.12 Extent of Exposure

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

### 9.7.4 Interim Analyses

No interim analyses were planned or conducted for this study.

### 9.7.5 Determination of Sample Size

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

[Table 22](#) describes the expected power to demonstrate a reduction on 5 primary BoExp 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 using the assumptions from PMI YVD-CS01-EU study (9) (ClinicalTrials.gov: ID: NCT00812279) and PMI ZRHX-EX-01 study (38) (ClinicalTrials.gov: ID: NCT01780714) given a sample size of 160 smokers (~80 in THS 2.2 Menthol, ~40 in mCC, and ~40 in the SA arm).

**Table 22 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%

Therefore subjects were enrolled into the study until there were 160 smokers in the FAS.

## 9.8 Changes in the Conduct of the Study or Planned Analyses

### 9.8.1 Changes in the Conduct of the Study

This study was conducted according to the final protocol (Version 5.0) dated 14 April 2014. Version 5 was created to correct inconsistencies, errors in the timings of



assessments, and typographical errors in the previous version of the protocol (Version 4.0 dated 14 January 2014).

Previous versions and the main reasons for amendment are defined below.

**Version 4.0** of the protocol, dated 14 January 2014 - The main change in this version of the protocol was the deletion of an exploratory objective and endpoint, which involved the investigation of inflammatory cytokines in nasal lavages. Additionally, an exploratory objective and endpoint, which involved describing the changes in levels of oxysterols, was added to the protocol.

**Version 3.0** of the protocol, dated 11 December 2013 – The main purpose of this amendment was to reflect additional COHb sampling for the purpose of adjustment of gas transfer values, as well as providing additional clarifications to Version 2.0. Additionally, the description of spirometry to assess full lung functions was updated to reflect that gas transfer and lung volume assessments were to be done pre-bronchodilator and to provide the sequence of assessments. An exclusion criteria of asthma condition ( $FEV_1/FVC < 0.75$  and reversibility in  $FEV_1 > 12\%$  [or  $> 200$  mL]) was added and medications which impact on CYP1A2 and CYP2A6 were clarified.

**Version 2.0** of the protocol, dated 19 November 2013 – The main change in this version of the protocol were to the inclusion/exclusion criteria, and additional clarification was added to the statistical methods. Changes and clarifications included an extra secondary objective for determining changes in lung function, the upper age limit was removed from inclusion criterion No. 2, an additional exclusion criterion was added to exclude subjects with a history of AEs linked to caffeine-containing drugs, the definition of non-compliance was added to Section 12.1.2 of the protocol, and Apo A1 and B were added to the protocol as CREs to evaluate.

**Version 1.0** of the protocol, dated 26 June 2013.

#### 9.8.2 Changes in the Planned Analyses

For the VAS, the paper scales used by the study sites were less than 100 mm in length. In order to minimize variability, the same trained person and CRA at each of the study sites measured the distance on the paper VAS using the same ruler to verify measurement. The measurement from the paper scale was then transformed back to a score on the 100 mm scale using the following formula:  $VAS\ value = (100/a)*b$ , where  $a$  = the total length of the VAS scale on paper and  $b$  = the width of the patient reported outcome on the VAS.

The following changes to the analyses planned in the protocol were:

- The study team was accidentally unblinded during the course of the study. The first version of the SAP was issued on 30 September 2013 prior to first subject's first



visit and shared with the FDA. The list of changes from version 1.0 are listed in Section 3.1 of the SAP. The impact of the changes on the interpretation was none and was not influenced by the unblinding. The blinded review roles were delegated for data review. No decision on population's assignment and data review was made in an unblinded manner.

- The analysis of the relationship between primary and secondary BoExp, CREs, and NEQ was no longer an objective of the study.
- Urinary BoExp, CREs, and NEQ were evaluated using concentration adjusted for creatinine only for the data collected from the 4-hour urine fraction.
- When investigating the concordance between the results for urinary BoExp, CREs, and NEQ in 24-hour urine collection and 4-hour urine fraction only the actual value of the concentration adjusted for creatinine was used.
- When investigating the urinary BoExp, CREs, and NEQ in subjects quitting smoking, the 4-hour fraction data was not used.

The following changes to the analyses planned in the SAP were made after the SAP was finalized:

- Full lung function data was specified to be analyzed by the Safety Population in the SAP. This was an oversight as the original intent for these data was to analyze them as an efficacy endpoint; therefore, a posthoc analysis was performed using a mixed model conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Figures for the arithmetic mean and 95% CI for the Safety Population and the PP Set were also provided, along with descriptive statistics for the PP Set.
- 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 CREs were analyzed for all available assessments and not only on Day 90 as specified in the SAP.
- Due to a low number of subjects who quit during the study, analysis of the biomarker data for those subjects was not performed as planned in the SAP and thus, Figure 15.1.2.29 and Table 15.2.4.69 were not provided ([Appendix 16.1.8](#), [Section 12.6.3.10](#)).
- In the SAP, it was planned for LS mean ratios (THS m2.2:mCC) of HST parameters to be calculated; however due to an oversight, LS mean differences (THS m2.2 - mCC) were calculated. Following production of final tables, figures, and listings, analysis as per SAP was performed and geometric means and 95% CIs for HST parameters are provided in [Appendix 15](#), [Table 15.2.4.42.1](#) and [Figure 15.1.2.10.1](#);



and statistical analysis of geometric LS means ratios with two-sided 95% CI are provided in [Appendix 15, Table 15.2.4.43.1](#).

In addition, the footnote of [Listing 15.3.6.13](#) 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](#); due to the minor nature of this error the footnote of the listing has not been corrected.





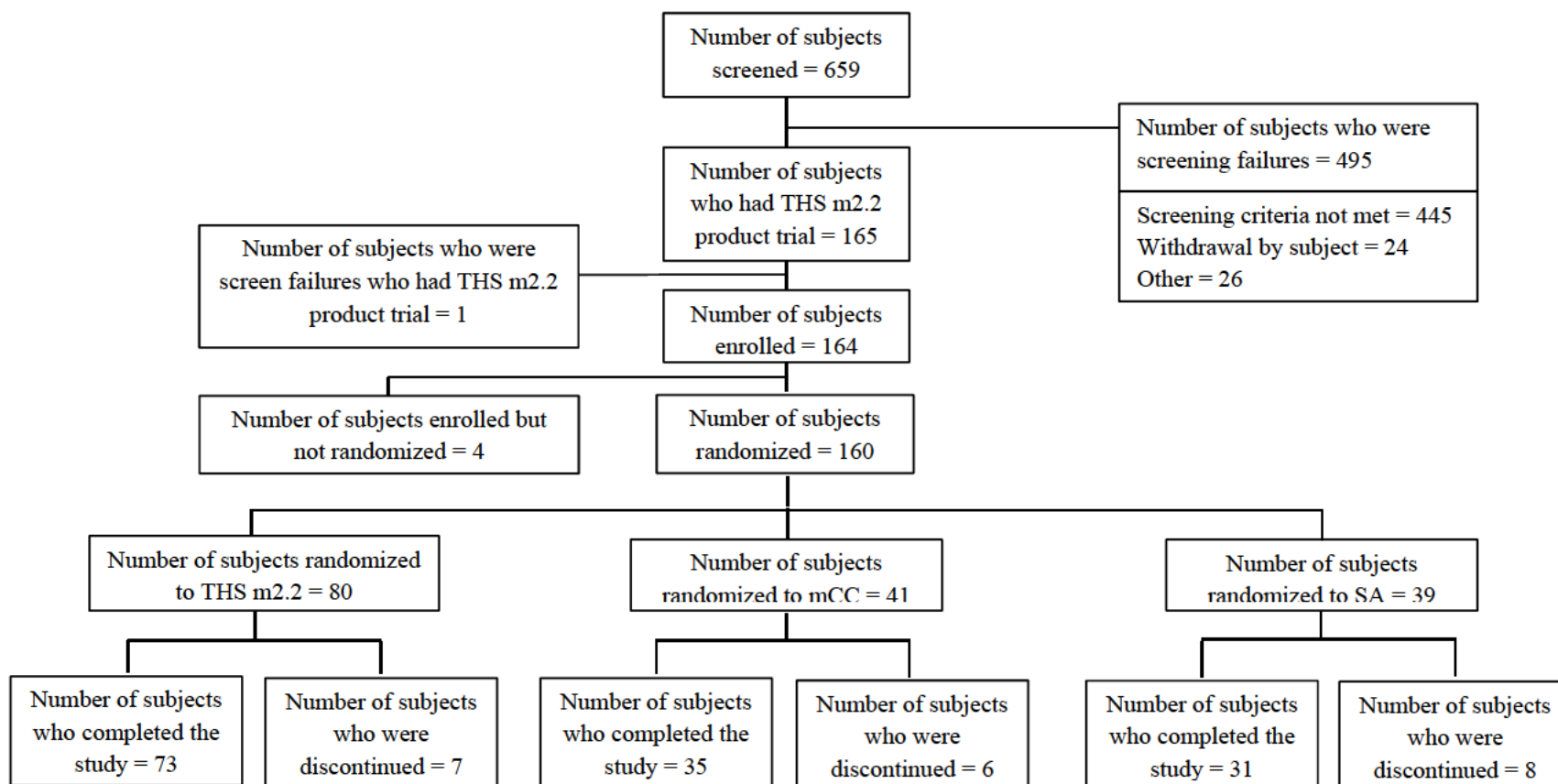
## 10 STUDY SUBJECTS

### 10.1 Disposition of Subjects

Subject disposition 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 Study Flow Chart**

Abbreviations: mCC = Menthol conventional cigarette; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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



Of the 659 subjects screened, 495 were screening failures and 165 went on to try the THS 2.2 Menthol product during the product trial. Of the 165 subjects who tried the THS 2.2 Menthol product, 4 subjects were discontinued from enrollment and were not randomized but completed the Safety Follow-up. One subject (Subject 1023) was a screening failure who was incorrectly allowed a THS 2.2 Menthol product test.

A total of 160 subjects were randomized, 80 subjects were randomized to the THS 2.2 Menthol arm, 41 subjects were randomized to the mCC arm, and 39 subjects were randomized to the SA arm.

Reasons for subject discontinuation are summarized for all subjects in [Table 23](#).

**Table 23 Subject Discontinuations - FAS**

	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Overall FAS (N=160)
Total number of discontinuations – n (%)	7 (8.8%)	6 (14.6%)	8 (20.5%)	21 (13.1%)
Reason for discontinuation				
Adverse events – n (%)	0	0	0	0
Protocol violation – n (%)	0	0	0	0
Withdrawal by subject – n (%)	2 (2.5%)	3 (7.3%)	6 (15.4%)	11 (6.9%)
Lost to follow-up – n (%)	3 (3.8%)	2 (4.9%)	0	5 (3.1%)
Physician decision – n (%)	1 (1.3%)	0	1 (2.6%)	2 (1.3%)
Other – n (%)	1 (1.3%)	1 (2.4%)	1 (2.6%)	3 (1.9%)

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

Percentages were calculated using the N in the column headers.

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

Overall in the FAS, 139 subjects completed all 4 periods of the study. Two, 3, and 6 subjects in the THS 2.2 Menthol, mCC, and SA arms, respectively, withdrew consent. Three subjects in the THS 2.2 arm and 2 subjects in the mCC arm were lost to follow-up, while 1 subject in each of the THS 2.2 Menthol and SA arms were discontinued due to the physician's decision. Three subjects were discontinued for other reasons; 1 subject in the THS 2.2 Menthol arm (unable to return as he lived out of state), 1 subject in the mCC arm (schedule clash with work), and 1 subject in the SA arm (due to the provider's discretion).

Of the 21 subjects that discontinued, 6 discontinued in Period 1, 2 discontinued in Period 2, 6 discontinued in Period 3, and 7 discontinued in Period 4.



## 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 are summarized in [Appendix 15, Table 15.2.1.3.1](#) and shown in [Table 24](#).

**Table 24 Protocol Deviations – Safety Population**

	THS m2.2 (N=80) n (%) events		mCC (N=41) n (%) events		SA (N=39) n (%) events		Overall Safety (N=160) n (%) events	
Major protocol deviations	47 (58.8%)	107	9 (22.0%)	10	34 (87.2%)	78	90 (56.3%)	195
With evaluability impact	47 (58.8%)	106	7 (17.1%)	7	33 (84.6%)	77	87 (54.4%)	190
Mis-randomization	4 (5.0%)	4	4 (9.8%)	4	5 (12.8%)	5	13 (8.1%)	13
Violation	0		1 (2.4%)	1	1 (2.6%)	1	2 (1.3%)	2
Other	1 (1.3%)	1	2 (4.9%)	2	0		3 (1.9%)	3
Misuse of product in Period 1	0		0		11 (28.2%)	11	11 (6.9%)	11
Misuse of product in Period 2	38 (47.5%)	38	0		19 (48.7%)	19	57 (35.6%)	57
Misuse of product in Period 3	37 (46.3%)	37	0		19 (48.7%)	19	56 (35.0%)	56
Misuse of product in Period 4	26 (32.5%)	26	0		22 (56.4%)	22	48 (30.0%)	48
Without evaluability impact	1 (1.3%)	1	3 (7.3%)	3	1 (2.6%)	1	5 (3.1%)	5
Violation	1 (1.3%)	1	2 (4.9%)	2	1 (2.6%)	1	4 (2.5%)	4
Other	0		1 (2.4%)	1	0		1 (0.6%)	1
Minor protocol deviations	79 (98.8%)	1642	41 (100.0%)	925	39 (100.0%)	464	159 (99.4%)	3031
Assessment missing	77 (96.3%)	609	40 (97.6%)	336	39 (100.0%)	180	156 (97.5%)	1125
Concomitant medication	0		1 (2.4%)	1	1 (2.6%)	2	2 (1.3%)	3
Time deviation	67 (83.8%)	491	36 (87.8%)	292	28 (71.8%)	117	131 (81.9%)	900
Time missing	26 (32.5%)	91	16 (39.0%)	48	8 (20.5%)	25	50 (31.3%)	164
Violation	70 (87.5%)	451	37 (90.2%)	248	31 (79.5%)	140	138 (86.3%)	839

Abbreviations: mCC = Menthol conventional cigarette; N = number of subjects randomized; n = number of subjects with deviations; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Percentages were calculated using the N in the column headers.  
Data Source: [Appendix 15, Table 15.2.1.3.1](#).





Major protocol deviations which were assessed to impact study primary objectives evaluability included mis-randomization (13 subjects were mis-stratified using Day -2 mCC use rather than Screening mCC use [see below and note to file in [Appendix 16.1.1, Section 16.1.1.3](#)]), misuse of the product, violations, and other deviations which were related to the collection of urine samples. The majority of major deviations reported were due to misuse of the product, i.e., subjects who were not compliant to the study arm they were randomized to; these deviations were taken into account when defining the PP Set and Compliant Population.

Thirteen subjects (4 subjects in the THS 2.2 Menthol arm, 4 in the mCC arm, and 5 in the SA arm) were randomized incorrectly at the Daytona Beach Clinical Research Unit due to site staff not following the protocol correctly (see below and note to file in [Appendix 16.1.1, Section 16.1.1.3](#)). Instead of using the cigarette consumption recorded at Screening, the cigarette consumption from Day -2 was used as a stratification factor for these subjects. However there was no imbalance in the 2:1 randomization ratio; the stratification was still balanced, and so accordingly it was confirmed that no sensitivity analysis would be performed other than that originally planned in the SAP (see note to file in [Appendix 16.1.1, Section 16.1.1.3](#)).

Major protocol deviations which were assessed not to have an impact on study evaluations included violations and deviations termed as Other (Day 3 urine sample for 1 subject was added to another subject's urine sample in error). Minor protocol deviations relating to violations, concomitant medication, missing assessments or times, or time schedule deviations were also reported.

### 10.3 Data Sets Analyzed

The number of subjects in each analysis set and reasons for exclusion are summarized in [Table 25](#).



**Table 25 Summary of Analysis Population Sets and Reasons for Exclusions from Analyses**

Population sets	THS m2.2 n (%)	mCC n (%)	SA n (%)	Product Screen		Overall n (%)
				Test n (%)	Failure n (%)	
<b>Screened</b>	<b>80</b>	<b>41</b>	<b>39</b>	<b>5</b>	<b>494</b>	<b>659</b>
<b>Safety Population</b>	<b>80</b>	<b>41</b>	<b>39</b>	<b>5</b>	<b>0</b>	<b>165</b>
Subjects excluded	0	0	0	0	494	494
Not exposed to THS m2.2	0	0	0	0	494	494
<b>Total subjects randomized</b>	<b>80</b>	<b>41</b>	<b>39</b>	<b>NA</b>	<b>NA</b>	<b>160</b>
<b>Safety Population</b>	<b>80 (100%)</b>	<b>41 (100%)</b>	<b>39 (100%)</b>			<b>160 (100%)</b>
Subject excluded	0	0	0			0
<b>FAS</b>	<b>80 (100%)</b>	<b>41 (100%)</b>	<b>39 (100%)</b>			<b>160 (100%)</b>
<b>PP Set</b>						
Period 1	75 (93.8%)	35 (85.4%)	24 (61.5%)			134 (83.8%)
Period 2	40 (50.0%)	34 (82.9%)	13 (33.3%)			87 (54.4%)
Period 3	39 (48.8%)	35 (85.4%)	12 (30.8%)			86 (53.8%)
Period 4	47 (58.8%)	32 (78.0%)	9 (23.1%)			88 (55.0%)
<b>Compliant Population</b>						
Period 1	75 (93.8%)	35 (85.4%)	24 (61.5%)			134 (83.8%)
Period 2	32 (40.0%)	34 (82.9%)	8 (20.5%)			74 (46.3%)
Period 3	36 (45.0%)	34 (82.9%)	7 (17.9%)			77 (48.1%)
Period 4	41 (51.3%)	31 (75.6%)	7 (17.9%)			79 (49.4%)

Abbreviations: mCC = Menthol conventional cigarettes; NA = Not applicable; 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.

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.](#)

The safety endpoints were analyzed using the Safety Population. The Safety Population before randomization (N=165) consisted of all enrolled subjects and one screening failure (Subject 1023) who was incorrectly allowed to complete a THS 2.2 Menthol product test. After randomization, the Safety Population consisted only of those subjects who had one valid post-randomization safety assessment (N=160).

The FAS (N=160) consisted of all randomized subjects who had at least one post-randomization product use experience (THS 2.2 Menthol and mCC arms) and had at least one valid non-safety assessment. The number of subjects in each study arm for this population was 80 subjects in the THS 2.2 Menthol study arm, 41 in the mCC study arm,



and 39 in the SA study arm. The FAS was the primary analysis set for compliance to randomization arm.

Two further population sets, the PP Set and the Compliant Population were also analyzed by study period. The PP Set included all randomized subjects who had no major protocol deviations impacting evaluability of the study's primary objectives. Within the PP Set, 4 subjects in the THS 2.2 Menthol arm, 4 subjects in the mCC arm, and 5 subjects in the SA arm were excluded from all periods because they were mis-randomized (see note to file in [Appendix 16.1.1](#), [Section 16.1.1.3](#) and [Section 10.2](#)). One subject in the THS 2.2 Menthol arm (Subject 1042) was excluded from all periods due to access being granted to their medical records for source data verification and data entry despite authorization of their protected health information being withdrawn ([Appendix 16.1.1](#), [Section 16.1.1.3](#)). A number of subjects were excluded from the PP Set for the THS 2.2 Menthol and SA arms as they were not compliant to their assigned randomization arm in each study period. In the THS 2.2 Menthol arm, the number of subjects in the PP Set decreased from 75 (93.8%) in Period 1 to 39 subjects (48.8%) in Period 3 before increasing to 47 subjects (58.8%) at Period 4. In the mCC arm, the number of subjects in the PP Set decreased from 35 subjects (85.4%) in Period 1 to 32 subjects (78.0%) in Period 4. In the SA arm, the number of subjects in the PP Set decreased from 24 subjects (61.5%) in Period 1 to 9 subjects (23.1%) in Period 4.

The Compliant Population was a subset of the PP Set and consisted only of those subjects who were exclusive users of THS 2.2 Menthol and mCC in those study arms, and subjects in the SA arm that were entirely abstinent. The lowest number of subjects in the Compliant Population for the THS 2.2 arm was 32 subjects (40.0%) in Period 2, and 7 subjects (17.9%) in the SA arm in Periods 3 and 4.

Within this report, the safety endpoints analyzed using the Safety Population pre- and post-randomization (165 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 enrolled, randomized, and in each study arm with the stratification factors are summarized in [Table 26](#).

**Table 26 Summary of Analysis Populations by Stratification Factors and Product**

Strata	FAS (N=160)				Overall Safety (N=165)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	FAS (N=160)	
Sex					
Male, n (%)	48 (60.0%)	24 (58.5%)	24 (61.5%)	96 (60.0%)	98 (59.4%)
Female, n (%)	32 (40.0%)	17 (41.5%)	15 (38.5%)	64 (40.0%)	67 (40.6%)
Daily cigarette consumption at Screening					
10 to 19 cig/day, n (%)	43 (53.8%)	21 (51.2%)	18 (46.2%)	82 (51.3%)	85 (51.5%)
>19 cig/day, n (%)	36 (45.0%)	20 (48.8%)	21 (53.8%)	77 (48.1%)	78 (47.3%)
Missing	1 (1.3%)	0	0	1 (0.6%)	2 (1.2%)

Abbreviations: cig = cigarette; FAS = Full Analysis Set; mCC = Menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = 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 CC consumption of 10 to 19 and >19 cigarettes/day was comparable between the THS 2.2 Menthol, mCC, and SA study arms in the FAS. 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 27](#), and the PP Set for each period in [Table 28, Table 29, Table 30, and Table 31](#).




**Table 27 Summary of Demographic Data – Safety Population and FAS**

Variable	Statistic	FAS				
		THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Overall Safety (N=165)	Overall FAS (N=160)
Sex						
Male	n (%)	48 (60.0%)	24 (58.5%)	24 (61.5)	98 (59.4%)	96 (60.0%)
Female	n (%)	32 (60.0%)	17 (41.5%)	15 (38.5%)	67 (40.6%)	64 (40.0%)
Race						
White	n (%)	49 (61.3%)	28 (68.3%)	22 (56.4%)	104 (63.0%)	99 (61.9%)
Black or African American	n (%)	23 (28.8%)	11 (26.8%)	17 (43.6%)	51 (30.9%)	51 (31.9%)
Other	n (%)	7 (8.8%)	2 (4.9%)	0	9 (5.5%)	9 (5.6%)
Missing	n (%)	1 (1.3%)	0	0	1 (0.6%)	1 (0.6%)
Age (years)	Mean (SD)	39.2 (11.72)	33.7 (10.17)	38.8 (11.42)	37.8 (11.34)	37.7 (11.45)
	Median	36.5	32.0	37.0	35.0	34.5
	Min, Max	22, 66	23, 60	22, 58	22, 66	22, 66
Height (m)	Mean (SD)	1.707 (0.0869) <sup>a</sup>	1.712 (0.0955)	1.707 (0.0890)	1.710 (0.0904) <sup>b</sup>	1.709 (0.0892) <sup>c</sup>
	Median	1.720	1.716	1.713	1.720	1.716
	Min, Max	1.49, 1.84	1.51, 1.89	1.53, 1.89	1.49, 1.89	1.49, 1.89
Weight (kg)	Mean (SD)	78.92 (13.893) <sup>a</sup>	75.59 (12.710)	76.52 (13.682)	77.94 (13.862) <sup>b</sup>	77.47 (13.542) <sup>c</sup>
	Median	78.60	73.70	74.70	76.90	76.50
	Min, Max	52.9, 115.3	49.3, 103.2	48.1, 121.2	48.1, 121.2	48.1, 121.2
BMI (kg/m <sup>2</sup> )	Mean (SD)	27.04 (4.105) <sup>a</sup>	25.75 (3.667)	26.20 (3.763)	26.62 (4.002) <sup>b</sup>	26.50 (3.930) <sup>c</sup>
	Median	26.80	25.30	25.60	26.60	26.50
	Min, Max	19.1, 34.9	18.6, 32.9	19.4, 34.3	18.6, 34.9	18.6, 34.9
Underweight	n (%)	0	0	0	0	0
Normal weight	n (%)	26 (32.5%)	18 (43.9%)	19 (48.7%)	64 (38.8%)	63 (39.4%)
Overweight	n (%)	32 (40.0%)	16 (39.0%)	13 (33.3%)	61 (37.0%)	61 (38.1%)

**Table 27 Summary of Demographic Data – Safety Population and FAS**

Variable	Statistic	FAS				
		THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Overall Safety (N=165)	Overall FAS (N=160)
Obese	n (%)	21 (26.3%)	7 (17.1%)	7 (17.9%)	38 (23.0%)	35 (21.9%)
Missing	n (%)	1 (1.3%)	0	0	2 (1.2%)	1 (0.6%)
Cigarette consumption						
10 to 19 cig/day	n (%)	43 (53.8%)	21 (51.2%)	18 (46.2%)	85 (51.5%)	82 (51.3%)
>19 cig/day	n (%)	36 (45.0%)	20 (48.8%)	21 (53.8%)	78 (47.3%)	77 (48.1%)
Missing	n (%)	1 (1.3%)	0	0	2 (1.2%)	1 (0.6%)

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

<sup>a</sup> N = 79; <sup>b</sup> N = 163; <sup>c</sup> N = 159.

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

**Table 28 Summary of Demographic Data – PP Set: Period 1**

Variable	Statistic	Overall PP Set (N=134)	THS m2.2 (N=75)	mCC (N=35)	SA (N=24)
Sex					
Male	n (%)	81 (60.4%)	46 (61.3%)	20 (57.1%)	15 (62.5%)
Female	n (%)	53 (39.6%)	29 (38.7%)	15 (42.9%)	9 (37.5%)
Race					
White	n (%)	83 (61.9%)	46 (61.3%)	24 (68.6%)	13 (54.2%)
Black or African American	n (%)	43 (32.1%)	22 (29.3%)	10 (28.6%)	11 (45.8%)
Other	n (%)	8 (6.0%)	7 (9.3%)	1 (2.9%)	0
Age (years)	Mean (SD)	38.0 (11.45)	39.0 (11.77)	34.1 (10.48)	40.5 (10.79)
	Median	34.5	36.0	32.0	40.0
	Min, Max	22, 66	22, 66	23, 60	22, 57
Height (m)	Mean (SD)	1.709 (0.0899)	1.708 (0.0867)	1.714 (0.0998)	1.707 (0.0882)
	Median	1.720	1.726	1.720	1.739
	Min, Max	1.49, 1.89	1.49, 1.84	1.51, 1.89	1.53, 1.85
Weight (kg)	Mean (SD)	77.92 (13.260)	79.42 (13.858)	76.58 (13.148)	75.18 (11.197)
	Median	77.15	78.70	75.40	74.10
	Min, Max	48.1, 115.3	52.9, 115.3	49.3, 103.2	48.1, 97.1
BMI (kg/m <sup>2</sup> )	Mean (SD)	26.65 (3.928)	27.19 (4.136)	26.06 (3.805)	25.79 (3.240)
	Median	26.70	27.10	26.10	24.60
	Min, Max	18.6, 34.9	19.1, 34.9	18.6, 32.9	20.6, 32.0
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	52 (38.8%)	24 (32.0%)	15 (42.9%)	13 (54.2%)
Overweight	n (%)	51 (38.1%)	30 (40.0%)	13 (37.1%)	8 (33.3%)
Obese	n (%)	31 (23.1%)	21 (28.0%)	7 (20.0%)	3 (12.5%)

**Table 28 Summary of Demographic Data – PP Set: Period 1**

Variable	Statistic	Overall PP Set (N=134)	THS m2.2 (N=75)	mCC (N=35)	SA (N=24)
Cigarette consumption					
10 to 19 cig/day	n (%)	76 (56.7%)	43 (57.3%)	20 (57.1%)	13 (54.2%)
>19 cig/day	n (%)	58 (43.3%)	32 (42.7%)	15 (42.9%)	11 (45.8%)

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 29 Summary of Demographic Data – PP Set: Period 2**

Variable	Statistic	Overall PP Set (N=87)	THS m2.2 (N=40)	mCC (N=34)	SA (N=13)
Sex					
Male	n (%)	53 (60.9%)	24 (60.0%)	21 (61.8%)	8 (61.5%)
Female	n (%)	34 (39.1%)	16 (40.0%)	13 (38.2%)	5 (38.5%)
Race					
White	n (%)	57 (65.5%)	30 (75.0%)	22 (64.7%)	5 (38.5%)
Black or African American	n (%)	29 (33.3%)	10 (25.0%)	11 (32.4%)	8 (61.5%)
Other	n (%)	1 (1.1%)	0	1 (2.9%)	0
Age (years)	Mean (SD)	36.9 (11.45)	38.9 (11.92)	33.4 (10.39)	40.2 (11.06)
	Median	33.0	34.5	31.0	38.0
	Min, Max	22, 66	24, 66	23, 60	22, 54
Height (m)	Mean (SD)	1.708 (0.0910)	1.699 (0.0915)	1.721 (0.0934)	1.698 (0.0858)
	Median	1.713	1.700	1.720	1.713
	Min, Max	1.49, 1.89	1.49, 1.84	1.53, 1.89	1.53, 1.83
Weight (kg)	Mean (SD)	76.88 (13.588)	78.82 (14.583)	77.02 (13.077)	70.55 (10.279)
	Median	76.90	79.35	76.15	72.70
	Min, Max	48.1, 108.7	52.9, 108.7	49.3, 103.2	48.1, 87.7
BMI (kg/m <sup>2</sup> )	Mean (SD)	26.34 (4.061)	27.26 (4.353)	25.98 (3.770)	24.48 (3.249)
	Median	26.60	27.15	25.80	24.20
	Min, Max	18.6, 34.4	19.1, 34.4	18.6, 32.9	19.4, 30.0
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	33 (37.9%)	11 (27.5%)	14 (41.2%)	8 (61.5%)
Overweight	n (%)	35 (40.2%)	17 (42.5%)	14 (41.2%)	4 (30.8%)
Obese	n (%)	19 (21.8%)	12 (30.0%)	6 (17.6%)	1 (7.7%)

**Table 29 Summary of Demographic Data – PP Set: Period 2**

Variable	Statistic	Overall PP Set (N=87)	THS m2.2 (N=40)	mCC (N=34)	SA (N=13)
Cigarette consumption					
10 to 19 cig/day	n (%)	44 (50.6%)	18 (45.0%)	19 (55.9%)	7 (53.8%)
>19 cig/day	n (%)	43 (49.4%)	22 (55.0%)	15 (44.1%)	6 (46.2%)

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 30 Summary of Demographic Data – PP Set: Period 3**

Variable	Statistic	Overall PP Set (N=86)	THS m2.2 (N=39)	mCC (N=35)	SA (N=12)
Sex					
Male	n (%)	53 (61.6%)	23 (59.0%)	21 (60.0%)	9 (75.0%)
Female	n (%)	33 (38.4%)	16 (41.0%)	14 (40.0%)	3 (25.0%)
Race					
White	n (%)	57 (66.3%)	29 (74.4%)	23 (65.7%)	5 (41.7%)
Black or African American	n (%)	27 (31.4%)	9 (23.1%)	11 (31.4%)	7 (58.3%)
Other	n (%)	2 (2.3%)	1 (2.6%)	1 (2.9%)	0
Age (years)	Mean (SD)	36.9 (11.35)	38.8 (12.05)	33.3 (10.24)	41.3 (9.87)
	Median	33.0	34.0	32.0	40.5
	Min, Max	23, 66	24, 66	23, 60	26, 54
Height (m)	Mean (SD)	1.709 (0.0914)	1.700 (0.0913)	1.718 (0.0939)	1.712 (0.0891)
	Median	1.716	1.700	1.720	1.739
	Min, Max	1.49, 1.89	1.49, 1.84	1.53, 1.89	1.53, 1.83
Weight (kg)	Mean (SD)	77.57 (14.376)	80.57 (15.677)	76.57 (13.155)	70.78 (11.306)
	Median	77.45	83.00	75.40	71.70
	Min, Max	48.1, 115.3	52.9, 115.3	49.3, 103.2	48.1, 87.7
BMI (kg/m <sup>2</sup> )	Mean (SD)	26.51 (4.219)	27.79 (4.542)	25.91 (3.736)	24.11 (3.145)
	Median	26.50	27.60	25.50	23.55
	Min, Max	18.6, 34.9	19.1, 34.9	18.6, 32.9	19.4, 30.0
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	33 (38.4%)	10 (25.6%)	15 (42.9%)	8 (66.7%)
Overweight	n (%)	32 (37.2%)	15 (38.5%)	14 (40.0%)	3 (25.0%)
Obese	n (%)	21 (24.4%)	14 (35.9%)	6 (17.1%)	1 (8.3%)

**Table 30 Summary of Demographic Data – PP Set: Period 3**

Variable	Statistic	Overall PP Set (N=86)	THS m2.2 (N=39)	mCC (N=35)	SA (N=12)
Cigarette consumption					
10 to 19 cig/day	n (%)	44 (51.2%)	16 (41.0%)	20 (57.1%)	8 (66.7%)
>19 cig/day	n (%)	42 (48.8%)	23 (59.0%)	15 (42.9%)	4 (33.3%)

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 31 Summary of Demographic Data – PP Set: Period 4**

Variable	Statistic	Overall PP Set (N=88)	THS m2.2 (N=47)	mCC (N=32)	SA (N=9)
Sex					
Male	n (%)	54 (61.4%)	28 (59.6%)	19 (59.4%)	7 (77.8%)
Female	n (%)	34 (38.6%)	19 (40.4%)	13 (40.6%)	2 (22.2%)
Race					
White	n (%)	58 (65.9%)	34 (72.3%)	20 (62.5%)	4 (44.4%)
Black or African American	n (%)	26 (29.5%)	10 (21.3%)	11 (34.4%)	5 (55.6%)
Other	n (%)	4 (4.5%)	3 (6.4%)	1 (3.1%)	0
Age (years)	Mean (SD)	36.6 (11.37)	37.6 (11.92)	34.0 (10.43)	40.7 (10.79)
	Median	33.0	33.0	32.0	38.0
	Min, Max	23, 66	24, 66	23, 60	26, 54
Height (m)	Mean (SD)	1.711 (0.0911)	1.702 (0.0900)	1.723 (0.0932)	1.713 (0.0946)
	Median	1.716	1.709	1.720	1.737
	Min, Max	1.49, 1.89	1.49, 1.84	1.53, 1.89	1.53, 1.83
Weight (kg)	Mean (SD)	77.35 (14.228)	78.94 (14.966)	77.64 (13.191)	67.97 (11.177)
	Median	77.15	78.80	77.70	68.40
	Min, Max	48.1, 115.3	52.9, 115.3	49.3, 103.2	48.1, 85.8
BMI (kg/m <sup>2</sup> )	Mean (SD)	26.39 (4.215)	27.23 (4.502)	26.11 (3.717)	23.07 (2.515)
	Median	26.55	27.10	25.80	23.10
	Min, Max	18.6, 34.9	19.1, 34.9	18.6, 32.9	19.4, 27.1
Underweight	n (%)	0	0	0	0
Normal weight	n (%)	33 (37.5%)	13 (27.7%)	13 (40.6%)	7 (77.8%)
Overweight	n (%)	35 (39.8%)	20 (42.6%)	13 (40.6%)	2 (22.2%)
Obese	n (%)	20 (22.7%)	14 (29.8%)	6 (18.8%)	0

**Table 31 Summary of Demographic Data – PP Set: Period 4**

Variable	Statistic	Overall PP Set (N=88)	THS m2.2 (N=47)	mCC (N=32)	SA (N=9)
Cigarette consumption					
10 to 19 cig/day	n (%)	46 (52.3%)	21 (44.7%)	19 (59.4%)	6 (66.7%)
>19 cig/day	n (%)	42 (47.7%)	26 (55.3%)	13 (40.6%)	3 (33.3%)

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.](#)



The majority of subjects in the FAS were white (61.9%), while 51 subjects were Black or African American (31.9%), 9 subjects were classed as “Other”, and 1 subject’s race was missing. The mean height, weight, and BMI at baseline were comparable between the THS 2.2 Menthol, mCC, and SA arms in the FAS. The mean age in the mCC study arm was lower than in the THS 2.2 Menthol and SA arms.

Due to the number of non-compliant subjects, the number of subjects in the PP Set was lower than the number of subjects in the FAS in each period. Therefore, the values for demography parameters differ based on the number of subjects being summarized in the PP Set for each period ([Appendix 15, Table 15.2.1.4.3](#)). The proportion of male and female subjects was comparable in each study arm in the FAS and PP Set for Periods 1 and 2 (approximately 60% male, 40% female). For the PP Set of Period 3 and Period 4, the proportion of male and female subjects was comparable to the PP Set of Periods 1 and 2 for the THS 2.2 Menthol and mCC arms; however, the proportion of female subjects had fallen to 25.0% and 22.2% in the PP Set of Period 3 and Period 4, respectively, in the SA arm. Mean age was lower in the mCC arm compared to the other study arms, however mean height, weight, and BMI were comparable between study groups in the PP Set of Periods 1, 2, 3, and 4.

The BMI data are further summarized by the following categories: underweight ( $<18.5 \text{ kg/m}^2$ ), normal weight ( $\geq 18.5$  to  $<25.0 \text{ kg/m}^2$ ), overweight ( $\geq 25.0$  to  $<30.0 \text{ kg/m}^2$ ), and obese ( $\geq 30.0 \text{ kg/m}^2$ ). The number of subjects in each BMI category was generally similar for each study arm at baseline and Periods 1, 2, 3, and 4; however, the number of subjects categorized as obese was lower in the SA study arm compared to THS 2.2 Menthol and mCC study arms throughout the study.

The proportion of subjects in each CC consumption category (10 to 19 cigarettes/day and  $>19$  cigarettes/day) was comparable for each study arm at baseline and Periods 1, 2, 3, and 4.

The data for the PP Set is further summarized by gender 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 33.0 to 38.3 years for males and from 35.6 to 44.3 years for females (PP Set Period 1). The mean BMI across the study arms at baseline ranged from 24.95 to 26.54  $\text{kg/m}^2$  for males and from 26.68 to 28.23  $\text{kg/m}^2$  for females. The overall number of subjects in the obese BMI category was similar between males and female, but the number of subjects for the normal weight and overweight categories varied between male and female subjects in each study arm.

The mean age across the study arms at baseline ranged from 32.6 to 39.2 years for subjects who smoked 10 to 19 cigarettes/day and 36.1 to 42.1 years for subjects who smoked  $>19$  cigarettes/day. The mean BMI across the study arms at baseline ranged from 25.61 to 26.66  $\text{kg/m}^2$  for subjects who smoked 10 to 19 cigarettes/day and from 25.61 to



27.92 kg/m<sup>2</sup> for subjects who smoked >19 cigarettes/day. The overall number of subjects in the normal weight BMI category was lower in the subjects who smoked >19 cigarettes/day compared to those who smoked 10 to 19 cigarettes/day.

Daily CC consumption of >19 cigarettes/day was similar between male and females in each study arm, but the number of male subjects who consumed 10 to 19 cigarettes/day was greater than females in each study arm.

#### 10.4.2 Medical and Surgical History

Medical history is presented 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 99 subjects (60.0%) reporting medical history findings; 51 subjects (63.8%) in the THS 2.2 Menthol study arm, 19 subjects (46.3%) in the mCC study arm, 26 subjects (66.7%) in the SA study, and 3 subjects (60.0%) who were enrolled and tested the study product but were not randomized.

The most frequent medical history findings by SOC were surgical and medical procedures (43 subjects [53.8%] in the THS 2.2 Menthol study arm, 16 subjects [39.0%] in the mCC study arm, and 20 subjects [51.3%] in the SA study arm), injury, poisoning, and procedural complications (16 subjects [20.0%] in the THS 2.2 Menthol study arm, 6 subjects [14.6%] in the mCC study arm, and 9 subjects [23.1%] in the SA study arm), then pregnancy, puerperium and perinatal conditions (14 subjects [17.5%] in the THS 2.2 Menthol study arm, 1 subject [2.4%] in the mCC study arm, and 5 subjects [12.8%] in the SA study arm); infections and infestations (8 subjects [10.0%] in the THS 2.2 Menthol study arm, 8 subjects [19.5%] in the mCC study arm, and 4 subjects [10.3%] in the SA study arm); and nervous system disorders (5 subjects [6.3%] in the THS 2.2 Menthol study arm, 0 subjects in the mCC study arm, and the SA study arm). All other SOCs were reported in less than 5 subjects in the overall Safety Population.

The most frequent medical history findings by PT were tooth extraction, delivery of a child, caesarean section, tonsillectomy, female sterilization, and hysterectomy.

Of those subjects 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 (Day 0) is listed by subject in [Appendix 15, Listing 15.3.6.20](#) and summarized for the PP Set and FAS in [Appendix 15, Table 15.2.4.62.1](#) and [Table 15.2.4.62.2](#), respectively.





No relevant differences were observed between the 3 study arms, with regard to baseline CYP2A6 activity in either the PP Set or FAS.

Randomized subjects in the PP Set with evaluable CYP2A6 data had a mean baseline CYP2A6 activity of 32.251% (SD = 13.1236%, minimum = 14.14%, maximum = 69.66%) for the THS 2.2 Menthol study arm, 31.785% (SD = 10.4456%, minimum = 12.61%, maximum = 60.39%) for the mCC study arm, and 29.272% (SD = 9.6946%, minimum = 13.32%, maximum = 65.22%) for the SA study arm.

#### 10.4.4 Fagerström Test for Nicotine Dependence

Individual subject responses to the FTND are presented by study arm in [Appendix 15, Listing 15.3.6.13](#).

The FTND overall classification is summarized by category (mild: 0 to 3; moderate: 4 to 6; severe: 7 to 10) 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 baseline (1 to 4) in [Appendix 15, Table 15.2.1.4.3](#). Data for the FAS and PP Sets for Period 1 and Period 4 are also provided in [Table 32](#), [Table 33](#), and [Table 34](#), respectively.

**Table 32 Fagerström Test of Nicotine Dependence (FAS)**

FTND Score	Study Arm		
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)
Mean	5.6	5.5	5.7
SD	2.25	1.67	2.14
Median	6.0	6.0	6.0
Min, Max	0, 10	1, 9	2, 9
Mild (n [%])	14 (17.5%)	4 (9.8%)	7 (17.9%)
Moderate (n [%])	35 (43.8%)	25 (61.0%)	18 (46.2%)
Severe (n [%])	31 (38.8%)	10 (24.4%)	14 (35.9%)
Missing (n [%])	0	2 (4.9%)	0

Abbreviations: FAS = Full Analysis Set; FTND = Fagerström Test of Nicotine Dependence; max = maximum; min = minimum; mCC = Menthol conventional cigarette; N = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

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

**Table 33 Fagerström Test of Nicotine Dependence (PP Set Period 1)**

FTND Score	Study Arm		
	THS m2.2 (N=75)	mCC (N=35)	SA (N=24)
Mean	5.7	5.5	5.5
SD	2.26	1.71	2.03
Median	6.0	6.0	6.0
Min, Max	0, 10	1, 9	2, 8
Mild (n [%])	13 (17.3%)	4 (11.4%)	5 (20.8%)
Moderate (n [%])	31 (41.3%)	21 (60.0%)	11 (45.8%)
Severe (n [%])	31 (41.3%)	9 (25.7%)	8 (33.3%)
Missing (n [%])	0	1 (2.9%)	0

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](#).

**Table 34 Fagerström Test of Nicotine Dependence (PP Set Period 4)**

FTND Score	Study Arm		
	THS m2.2 (N=47)	mCC (N=32)	SA (N=9)
Mean	5.8	5.6	5.9
SD	2.22	1.70	2.37
Median	6.0	6.0	6.0
Min, Max	1, 10	1, 9	2, 8
Mild (n [%])	7 (14.9%)	3 (9.4%)	2 (22.2%)
Moderate (n [%])	19 (40.4%)	20 (62.5%)	3 (33.3%)
Severe (n [%])	21 (44.7%)	9 (28.1%)	4 (44.4%)

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 in the FAS, the majority of subjects were classified as either moderate or severe (43.8% and 38.8%, respectively) in the THS 2.2 Menthol arm (N=80), with 17.5% classified as mild; in the mCC arm (N=41), 61.0% were classified as moderate, with 9.8% and 24.4% classified as mild and severe, respectively; and in the SA arm (N=39), 46.2% were classified as moderate, with 17.9% and 35.9% classified as mild and severe, respectively.

In the PP Set for Periods 2, 3, and 4, the proportions of subjects classified as mild, moderate, and severe were comparable to PP Set for Period 1 for the THS 2.2 Menthol and mCC arms. For the SA arm, the proportion of subjects classified as severe was 61.5%



(8 out of 13 subjects) in the PP Set of Period 2, and 41.7% and 44.4% for the PP Set in Periods 3 and 4, respectively (5 out of 12 and 4 out of 9 subjects, respectively).

The results of the overall Safety Population were consistent with the FAS and PP Set at baseline, with the majority of the subjects classified as having a moderate dependence on nicotine (49.1%).

#### 10.4.5 Socio-economic Status Questionnaire

Individual subject responses to the SES questionnaire are presented by study arm in [Appendix 15, Listing 15.3.1.11](#).

The SES educational attainment, annual household income, and composite questionnaire results are summarized by category (low, moderate, and high) 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 SES data are summarized as above for the PP Set for each period baseline (1 to 4) in [Appendix 15, Table 15.2.1.4.3](#).

In the FAS, the majority of subjects (58.1%) had a high educational attainment, with 28.8% and 8.8% of subjects having moderate and low educational attainment, respectively. Seven subjects did not answer the questionnaire (4.4%). The distribution of educational attainment was comparable in the THS 2.2 Menthol, mCC, and SA arms.

One hundred and twenty-three of the 160 subjects (76.9%) in the FAS responded to the annual household income part of the SES questionnaire, and the percentages discussed in this section refer to the total number of subjects in each population rather than the percentage of responders to the questionnaire. In the FAS, a greater percentage of subjects had a low annual income (38.1%) compared to those with a moderate (23.1%), or high household income (15.6%). The distribution of household incomes was comparable to the overall FAS for the THS 2.2 Menthol and SA arms, while the mCC arm had a higher proportion of low annual income (43.9%), and a lower proportion of moderate (17.1%) and high (12.2%) annual income compared to the overall FAS.

In the FAS, the SES composite measure showed an identical proportion of high and moderate subjects (36.9%), while 3.1% of subjects were classed as low. The distribution of SES composite categories was comparable to the overall FAS for all study arms.

#### 10.4.6 Current Cigarette Brand Consumption

The current mCC brand(s) smoked by the subject, as recorded at the Screening Visit and on Day -2, are listed by study arm in [Appendix 15, Listing 15.3.1.2](#).

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



#### 10.4.7 Smoking History and Willingness to Quit Smoking

Smoking history responses (including “plan to quit smoking in next 3 months” responses) at the Screening Visit 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. The number of subjects who smoked 10 to 19 and >19 cigarettes/day at baseline are summarized in [Table 26](#) in [Section 10.3](#).

#### 10.4.8 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 but 18 subjects at Screening. Abnormal X-rays were not considered to be CS by the Investigator and the subjects were considered suitable for enrollment.
- Urine cotinine screen at the Screening Visit were positive for all enrolled subjects.
- Urine drug screen and alcohol urine/breath test at the Screening Visit and on Day -2 were negative for all enrolled subjects.
- Serology tests at the Screening Visit: tests for HIV, HbsAg, and hepatitis C virus were negative or within the reference range for all enrolled subjects.
- Urine pregnancy test results at the Screening Visit, Admission (Day -2), and on the Day of Discharge were negative for all 67 female subjects in the overall Safety Population or the female was confirmed post-menopausal.

#### 10.4.9 Concomitant Diseases

Concomitant diseases are presented 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 35](#).





**Table 35 Concomitant Diseases by System Organ Class (Safety Population)**

System Organ Class	Study Arm				Overall Safety (N=165)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Product Test (N=5)	
Number (%) subjects with any concomitant disease	50 (62.5%)	25 (61.0%)	26 (66.7%)	2 (40.0%)	103 (62.4%)
Eye disorders	18 (22.5%)	9 (22.0%)	12 (30.8%)	0	39 (23.6%)
Immune system disorders	15 (18.8%)	10 (24.4%)	8 (20.5%)	1 (20.0%)	34 (20.6%)
Social circumstances	7 (8.8%)	2 (4.9%)	7 (17.9%)	2 (40.0%)	18 (10.9%)
Skin and subcutaneous tissue disorders	8 (10.0%)	5 (12.2%)	4 (10.3%)	0	17 (10.3%)
Gastrointestinal disorders	4 (5.0%)	4 (9.8%)	6 (15.4%)	1 (20.0%)	15 (9.1%)
Injury, poisoning, and procedural complications	3 (3.8%)	6 (14.6%)	1 (2.6%)	1 (20.0%)	11 (6.7%)
Nervous system disorders	4 (5.0%)	4 (9.8%)	2 (5.1%)	0	10 (6.1%)
Investigations	3 (3.8%)	4 (9.8%)	1 (2.6%)	0	8 (4.8%)
Reproductive system and breast disorders	3 (3.8%)	1 (2.4%)	3 (7.7%)	0	7 (4.2%)
Respiratory, thoracic, and mediastinal disorders	2 (2.5%)	4 (9.8%)	0	0	6 (3.6%)
Musculoskeletal and connective tissue disorders	2 (2.5%)	0	3 (7.7%)	0	5 (3.0%)
Metabolism and nutrition disorders	0	1 (2.4%)	2 (5.1%)	1 (20.0%)	4 (2.4%)
Surgical and medical procedures	3 (3.8%)	0	0	0	3 (1.8%)
Neoplasms benign, malignant, and unspecified	1 (1.3%)	0	1 (2.6%)	0	2 (1.2%)
Cardiac disorders	1 (1.3%)	0	1 (2.6%)	0	2 (1.2%)
Congenital, familial, and genetic disorders	2 (2.5%)	0	0	0	2 (1.2%)
Infections and infestations	1 (1.3%)	0	1 (2.6%)	0	2 (1.2%)
Psychiatric disorders	0	1 (2.4%)	1 (2.6%)	0	2 (1.2%)
Renal and urinary disorders	0	2 (4.9%)	0	0	2 (1.2%)
Endocrine disorders	0	1 (2.4%)	0	1 (0%)	1 (0.6%)
General disorders and administration site conditions	0	0	1 (2.6%)	1 (0%)	1 (0.6%)
Vascular disorders	0	1 (2.4%)	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 in the column headers.

Data Source: [Appendix 15, Table 15.2.1.7](#).



For the overall Safety Population (N=165), 103 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 comparable in the THS 2.2 Menthol, mCC, and SA study arms.

The most frequent concomitant disease by PT were myopia (5 subjects [6.3%] in the THS 2.2 Menthol arm, 5 subjects [12.2%] in the mCC arm, and 7 subjects [17.9%] in the SA arm); seasonal allergy (7 subjects [8.8%] in the THS 2.2 Menthol arm, 7 subjects [17.1%] in the mCC arm, and 3 subjects [7.7%] in the SA arm); presbyopia (7 subjects [8.8%] in the THS 2.2 Menthol arm, 2 subjects [4.9%] in the mCC arm, and 3 subjects [7.7%] in the SA arm); drug hypersensitivity (6 subjects [7.5%] in the THS 2.2 Menthol arm, 2 subjects [4.9%] in the mCC arm, and 3 subjects [7.7%] in the SA arm); and acne (7 subjects [8.8%] in the THS 2.2 arm, 4 subjects [9.8%] in the mCC arm, and 1 subject [2.6%] in the SA arm).

#### 10.4.10 Prior and Concomitant Medications

Prior and concomitant medications are listed for all subjects in [Appendix 15, Listing 15.3.6.4](#).

Prior and concomitant medications 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](#).

Concomitant medications taken during the pre-randomization period are summarized in [Table 36](#).

A total of 73 prior/concomitant medications were used in the pre-randomization period, 35 of which were used by 1 subject who completed the product test but was not randomized into the study (Subject 1119). Thirty-three of the 35 medications were administered for the treatment of an AE of diabetic ketoacidosis precipitated by sinusitis with glucose administered for low blood sugar and metformin given for treatment of type II diabetes. Further details are provided in [Section 12.2.2](#).

The incidence of prior/concomitant medication use during the pre-randomization period was low and comparable across THS 2.2 Menthol, mCC, and SA study arms.

**Table 36 Prior and Concomitant Medications: Pre-randomization (Safety Population)**

ATC1 ATC2	Study Arm				Overall Safety (N=165)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Product Test (N=5)	
Number (%) subjects with any prior/concomitant medication	14 (17.5%)	6 (14.6%)	8 (20.5%)	1 (20.0%)	29 (17.6%)
Genito urinary system and sex hormones	6 (7.5%)	1 (2.4%)	3 (7.7%)	0	10 (6.1%)
Sex hormones and modulators of the genital system	5 (6.3%)	1 (2.4%)	2 (5.1%)	0	8 (4.9%)
Other gynecologicals	1 (1.3%)	0	0	0	1 (0.6%)
Urologicals	0	0	1 (2.6%)	0	1 (0.6%)
Alimentary tract and metabolism	5 (6.3%)	1 (2.4%)	2 (5.1%)	1 (20.0%)	9 (5.5%)
Vitamins	4 (5.0%)	1 (2.4%)	1 (2.6%)	0	6 (3.6%)
Drugs for acid related disorders	0	0	1 (2.6%)	1 (20.0%)	2 (1.2%)
Mineral supplements	1 (1.3%)	0	0	1 (20.0%)	2 (1.2%)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	0	1 (2.4%)	0	0	1 (0.6%)
Antiemetics and antinauseants	0	0	0	1 (20.0%)	1 (0.6%)
Drugs for constipation	0	0	0	1 (20.0%)	1 (0.6%)
Drugs for functional gastrointestinal disorders	0	0	0	1 (20.0%)	1 (0.6%)
Drugs used in diabetes	0	0	0	1 (20.0%)	1 (0.6%)
Other alimentary tract and metabolism products	0	1 (2.4%)	0	0	1 (0.6%)
Nervous system	0	2 (4.9%)	3 (7.7%)	1 (20.0%)	6 (3.6%)
Analgesics	0	2 (4.9%)	2 (5.1%)	1 (20.0%)	5 (3.0%)
Other nervous system drugs	0	0	1 (2.6%)	0	1 (0.6%)
Psycholeptics	0	0	0	1 (20.0%)	1 (0.6%)
Respiratory system	1 (1.3%)	2 (4.9%)	0	1 (20.0%)	4 (2.4%)
Nasal preparations	1 (1.3%)	1 (2.4%)	0	1 (20.0%)	3 (1.8%)
Antihistamines for systemic use	0	1 (2.4%)	0	1 (20.0%)	2 (1.2%)
Anti-infectives for systemic use	1 (1.3%)	0	2 (5.1%)	1 (20.0%)	4 (2.4%)
Antibacterials for systemic use	1 (1.3%)	0	1 (2.6%)	1 (20.0%)	3 (1.8%)
Antivirals for systemic use	0	0	1 (2.6%)	0	1 (0.6%)
Various	1 (1.3%)	0	0	1 (20.0%)	2 (1.2%)
General nutrients	1 (1.3%)	0	0	1 (20.0%)	2 (1.2%)
Blood and blood forming organs	0	0	0	1 (20.0%)	1 (0.6%)
Antithrombotic agents	0	0	0	1 (20.0%)	1 (0.6%)



**Table 36 Prior and Concomitant Medications: Pre-randomization (Safety Population)**

ATC1 ATC2	Study Arm				Overall Safety (N=165)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Product Test (N=5)	
Blood substitutes and perfusion solutions	0	0	0	1 (20.0%)	1 (0.6%)
Cardiovascular system	0	1 (2.4%)	0	0	1 (0.6%)
Lipid modifying agents	0	1 (2.4%)	0	0	1 (0.6%)
Dermatologicals	0	0	1 (2.6%)	0	1 (0.6%)
Antibiotics and chemotherapeutics for dermatological use	0	0	1 (2.6%)	0	1 (0.6%)
Sensory organs	1 (1.3%)	0	0	0	1 (0.6%)
Ophthalmologicals	1 (1.3%)	0	0	0	1 (0.6%)
Systemic hormonal preparations, excluding sex hormones and insulins	0	1 (2.4%)	0	0	1 (0.6%)
Thyroid Therapy	0	1 (2.4%)	0	0	1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic and 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 in the column headers.

Data Source: [Appendix 15, Table 15.2.6.19.1](#).

Concomitant medications taken during the randomization period are summarized in [Table 37](#).



**Table 37 Concomitant Medications: Randomization (Safety Population)**

ATC1 ATC2	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	
Number (%) subjects with any concomitant medication	14 (17.5%)	9 (22.0%)	15 (38.5%)	38 (23.8%)
Nervous system	5 (6.3%)	2 (4.9%)	14 (35.9%)	21 (13.1%)
Analgesics	5 (6.3%)	2 (4.9%)	5 (12.8%)	12 (7.5%)
Other nervous system drugs	0	0	10 (25.6%)	10 (6.3%)
Respiratory system	4 (5.0%)	4 (9.8%)	1 (2.6%)	9 (5.6%)
Nasal preparations	2 (2.5%)	2 (4.9%)	0	4 (2.5%)
Cough and cold preparations	2 (2.5%)	1 (2.4%)	0	3 (1.9%)
Antihistamines for systemic use	0	1 (2.4%)	1 (2.6%)	2 (1.3%)
Alimentary tract and metabolism	3 (3.8%)	0	1 (2.6%)	4 (2.5%)
Drugs for acid related disorders	2 (2.5%)	0	0	2 (1.3%)
Stomatological preparations	1 (1.3%)	0	1 (2.6%)	2 (1.3%)
Dermatologicals	1 (1.3%)	2 (4.9%)	1 (2.6%)	4 (2.5%)
Antiseptics and disinfectants	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Antipruritics, including antihistamines, anesthetics, etc.	0	1 (2.4%)	0	1 (0.6%)
Emollients and protectives	0	0	1 (2.6%)	1 (0.6%)
Musculoskeletal system	0	1 (2.4%)	2 (5.1%)	3 (1.9%)
Anti-inflammatory and antirheumatic products	0	1 (2.4%)	1 (2.6%)	2 (1.3%)
Muscle relaxants	0	0	1 (2.6%)	1 (0.6%)
Anti-infectives for systemic use	2 (2.5%)	1 (2.4%)	0	3 (1.9%)
Antibacterials for systemic use	2 (2.5%)	0	0	2 (1.3%)
Vaccines	0	1 (2.4%)	0	1 (0.6%)
Genito urinary system and sex hormones	1 (1.3%)	0	0	1 (0.6%)
Urologicals	1 (1.3%)	0	0	1 (0.6%)
Sensory organs	0	0	1 (2.6%)	1 (0.6%)
Otologicals	0	0	1 (2.6%)	1 (0.6%)
Various	1 (1.3%)	0	0	1 (0.6%)
All other therapeutic products	1 (1.3%)	0	0	1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic and 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 in the column headers.  
Data Source: [Appendix 15, Table 15.2.6.19.1](#).



The incidence of concomitant medication use was comparable between the THS 2.2 Menthol and mCC arms. The incidence of concomitant medication use was higher in the SA arm, with 15 subjects using 24 concomitant medications. The majority of these were other nervous system drugs (ATC2) and were nicotine replacement therapies (10 subjects, 12 events).

Other commonly used concomitant medications during the randomization period were analgesics, nasal preparations, cough and cold preparations, drugs for acid related disorders, and antibacterials for systemic use. All other concomitant medications were taken by a maximum of 1 subject in each study arm.

There were a number of medications administered during the study which are known to have an impact on either 11-DTX-B2, CYP1A2, or CYP2A6. Analysis of these biomarkers 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 presented 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 presented in [Appendix 15, Listing 15.3.2.1.2](#). Details of product usage during the Ambulatory Period are presented in [Appendix 15, Listing 15.3.2.1.3](#).

Descriptive statistics of 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 Sets. 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 presented 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.

Details of product compliance during the study are reported in [Section 10.6](#).

The majority of enrolled subjects (136 subjects, 85.0%) completed the product test at Admission (Day -2) using only 1 THS Menthol Tobacco Stick, while 18 subjects (11.3%) used 2 sticks, 3 subjects (1.9%) used 3 sticks, and 1 subject (0.6%) used 4 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 38](#).

**Table 38**      **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	Mean (SD)	Min	Median	Max
THS m2.2	Day 0					
	(baseline, mCC use)	75	12.2 (3.68)	6	11.0	20
	Day 1	75	12.5 (4.68)	3	12.0	23
	Day 2	75	13.7 (4.96)	3	12.0	26
	Day 3	75	15.0 (5.27)	3	14.0	28
	Day 4	75	14.6 (5.19)	1	14.0	26
	Day 5	75	16.5 (5.77)	2	16.0	31
mCC	Day 0 (baseline)	35	12.2 (3.01)	6	12.0	19
	Day 1	35	11.5 (3.28)	4	11.0	19
	Day 2	34	12.0 (3.68)	6	11.5	21
	Day 3	34	12.2 (3.27)	7	12.0	20
	Day 4	34	11.9 (3.25)	7	11.5	18
	Day 5	34	13.7 (4.11)	7	14.0	23

Abbreviations: Max = maximum; mCC = Menthol conventional cigarette; Min = minimum; PP = per protocol; SD = standard deviation; 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 in the THS 2.2 Menthol study arm was comparable to the mean daily mCC consumed in the mCC study arm (Day 0, 12.2 and 12.2 cigarettes/day, respectively).

In the THS 2.2 Menthol arm, the mean number of THS Menthol Tobacco Sticks consumed daily gradually increased from Day 1 (12.5 sticks/day) to Day 5 (16.5 sticks/day) in the Confinement Period. The mean number of mCC consumed daily was stable throughout the Confinement Period in the mCC arm.

The average reported daily number of THS Menthol Tobacco Sticks and mCC/CC consumed during the Ambulatory Period are summarized for each period in [Table 39](#).



**Table 39 Number of THS Menthol Tobacco Sticks and Menthol Conventional Cigarettes/Conventional Cigarettes Consumed Daily in the Ambulatory Period**

Study Arm	Visit	Number of Subjects	Mean (SD) <sup>2</sup>	Min	Median	Max
<b>Safety Population<sup>1</sup></b>						
THS m2.2	Period 2	78	11.68 (7.103)	0.1	10.19	35.8
	Period 3	77	12.90 (9.090)	0.0	11.60	58.0
	Period 4	74	12.02 (7.195)	0.0	11.19	30.2
mCC	Period 2	40	14.96 (5.510)	2.9	14.94	31.0
	Period 3	36	15.51 (5.802)	2.7	14.63	29.6
	Period 4	35	15.79 (5.562)	8.6	14.93	32.4
<b>PP Set</b>						
THS m2.2	Period 2	39	14.73 (6.068)	3.1	14.42	35.5
	Period 3	39	15.18 (6.950)	0.0	15.59	33.5
	Period 4	47	14.21 (7.027)	0.0	14.38	30.2
mCC	Period 2	34	14.91 (5.854)	2.9	14.94	31.0
	Period 3	32	15.36 (6.124)	2.7	14.32	29.6
	Period 4	31	15.50 (5.840)	8.6	14.34	32.4

Abbreviations: CC = conventional cigarettes; 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.

[2] Mean number of THS Menthol Tobacco Sticks 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.](#)

The number of THS Menthol Tobacco Sticks used in the THS 2.2 Menthol arm and number of mCC/CC used in the mCC arm was relatively stable throughout the Ambulatory Period for both the Safety Population and the PP Set. In the Safety Population, the average reported daily number of THS Menthol Tobacco Sticks used was lower compared to the number of mCC/CC used in the mCC arm in each period.

The average reported daily number of THS Menthol Tobacco Sticks used in the THS 2.2 Menthol arm was higher in the PP Set compared to the Safety Population, and was comparable to the average daily number of mCC/CC used in the Safety Population and PP Set.

## 10.6 Compliance to Investigational Product

Compliance to the assigned products in each study arm and overall is presented for the FAS in [Appendix 15, 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

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.

In addition, in subjects in the SA arm, compliance was chemically verified in Confinement using an exhaled CO breath test. The cut-off point for the CO breath test value to distinguish mCC use versus SA use was 10 ppm. Compliance, as measured by exhaled CO during the Confinement Period is summarized for the FAS in [Appendix 15, Table 15.2.5.1](#).

Compliance to product use is summarized in [Table 40](#). The summaries for exclusive product use are based on the Compliant Population criterion, which is a subset of PP Set subjects, so even though all subjects exclusively used THS 2.2 Menthol or mCC, respectively, for the THS 2.2 Menthol and mCC arms in Period 1, some subjects were not counted as exclusive because they were not part of the PP Set in Period 1. A number of these subjects were excluded from the PP Set due to mis-randomization as 13 subjects were randomized using Day -2 mCC use rather than Screening mCC use (see [Section 10.2](#)).

In the THS 2.2 Menthol arm, 75 of 80 subjects had exclusive use of the THS 2.2 Menthol product during the Confinement Period. Of the 5 subjects in the THS 2.2 Menthol arm that were not included in the PP Set Population, 4 subjects were misrandomized and therefore had not been considered to be compliant and were excluded from the PP Set.

In the mCC arm, 35 of 41 subjects had exclusive use of mCC during the Confinement Period. Of the 6 subjects in the mCC arm that were not included in the PP Set Population, 4 subjects were misrandomized, and therefore had not been considered to be compliant and were excluded from the PP Set.

In the SA arm, 24 of 39 subjects were abstinent during the Confinement Period, 15 subjects were classed as not abstinent. All assessed subjects in the SA arm had exhaled CO levels below 10 ppm on Days 2, 3, 4, and 5, with the exception of 1 subject on Day 2 between 12:00 and 01:30 PM. However, on Day 6/Discharge Confinement, 5/32 subjects had exhaled CO levels >10 ppm ([Appendix 15, Table 15.2.5.1](#)). In addition, 11 subjects did not meet the PP criteria. Of the 11 subjects in the SA arm that were not included in the PP Set Population, 5 subjects were misrandomized, and therefore had not been considered to be compliant and were excluded from the PP Set.

**Table 40 Summary of Compliance by Period and Overall – FAS**

Compliance	Confinement		Ambulatory		Overall FAS
	Period 1	Period 2	Period 3	Period 4	
<b>THS m2.2 – N</b>	<b>80</b>	<b>80</b>	<b>80</b>	<b>80</b>	<b>80</b>
Exclusive product use <sup>1</sup> – n (%)					
Yes	75 (93.8%)	32 (40.0%)	36 (45.0%)	41 (51.3%)	24 (30.0%)
No	5 (6.3%)	48 (60.0%)	44 (55.0%)	39 (48.8%)	56 (70.0%)
PP criterion <sup>2</sup> – n (%)					
Yes	80 (100%)	42 (52.5%)	42 (52.5%)	50 (62.5%)	35 (43.8%)
No	0	38 (47.5%)	38 (47.5%)	30 (37.5%)	45 (56.3%)
<b>mCC – N</b>	<b>41</b>	<b>41</b>	<b>41</b>	<b>41</b>	<b>41</b>
Exclusive product use <sup>1</sup> – n (%)					
Yes	35 (85.4%)	34 (82.9%)	34 (82.9%)	31 (75.6%)	29 (70.7%)
No	6 (14.6%)	7 (17.1%)	7 (17.1%)	10 (24.4%)	12 (29.3%)
<b>SA – N</b>	<b>39</b>	<b>39</b>	<b>39</b>	<b>39</b>	<b>39</b>
Abstinent <sup>1</sup> – n (%)					
Yes	24 (61.5%)	8 (20.5%)	7 (18.0%)	7 (18.0%)	5 (12.8%)
No	15 (38.5%)	31 (79.5%)	32 (82.1%)	32 (82.1%)	34 (87.2%)
PP criterion <sup>2</sup> – n (%)					
Yes	28 (71.8%)	15 (38.5%)	14 (35.9%)	11 (28.2%)	8 (20.5%)
No	11 (28.2%)	24 (61.5%)	25 (64.1%)	28 (71.8%)	31 (79.5%)

Abbreviations: CC = conventional cigarettes; FAS = Full Analysis Set; mCC = Menthol conventional cigarette; N = number of subjects in the FAS for each arm; n = number of subjects; PP = per protocol; SA = smoking abstinence; 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]: 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). (Criterion for Compliant Population)

[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 Period.

Data Source: [Appendix 15, Tables 15.2.5.2.](#)



### 10.6.2 Compliance to Investigational Product During the Ambulatory Period

In the THS 2.2 Menthol arm 32, 36, and 41 of the 80 subjects exclusively used THS 2.2 Menthol during Periods 2, 3, and 4, respectively, and 24 of the 80 subjects exclusively used THS 2.2 Menthol in the study overall. Thirty-eight, 38, and 30 subjects did not meet the PP criteria of 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 Period in Periods 2, 3, and 4, respectively. Overall, 45 subjects did not meet the PP criteria in the THS 2.2 Menthol arm during the study.

In the mCC arm, 34, 34, and 31 subjects exclusively used mCC/CC in Periods 2, 3, and 4, and 29 subjects overall.

In the SA arm, 8, 7, and 7 of the 39 subjects were abstinent during Periods 2, 3, and 4, respectively, and 5 of the 39 subjects were abstinent overall. Twenty-four, 25, and 28 subjects did not meet the PP criteria in Periods 2, 3, and 4, respectively, and 31 subjects overall.

#### 10.6.2.1 Product Use by Product Use Category

A summary of product use by product use category is presented in [Appendix 15](#), [Table 15.2.2.4](#) and [Table 41](#).

In addition to the above compliance assessment, classification of subject's product use during the Ambulatory Period was also assessed ([Table 41](#)).

Of the 80 subjects in the THS 2.2 Menthol study arm, at least 72.5% within each period and over the entire Ambulatory Period for the FAS were classified as THS 2.2 Menthol users, using the THS 2.2 Menthol product at least 70% of the time; at least 57.5% subjects were classified as primarily THS 2.2 Menthol users, using the THS 2.2 Menthol product  $\geq 95\%$  of the time; and at least 33.8% were classified as exclusively THS 2.2 Menthol users, using the THS 2.2 Menthol product 100% of the time. Between 11 and 12 subjects in each period were considered to be dual balanced users, using the THS 2.2 Menthol device between 30% and 70% of the time. Between 5 and 6 subjects in each period were classified as mCC/CC users, using the THS 2.2 Menthol product  $\leq 30\%$  of the time.

Of the 41 subjects in the mCC arm, between 36 and 40 subjects who completed the study used mCC/CC exclusively in each period. One subject in Periods 3 and 4 was a dual user of both mCC/CC and other products.

In the SA arm, only 7 to 9 of the 39 subjects were abstinent in each period, with 6 subjects abstinent for the entire Ambulatory Period. The majority of subjects (21 to 22 subjects in each period) in the SA arm were classified as not abstinent.

**Table 41 Summary of Product Use by Product Use Category in Ambulatory Period - FAS**

Study Arm	Product Use Categorization	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)	Ambulatory n (%)
THS m2.2 Arm (N=80)	<b>THS m2.2 ([70-100]%)</b>	64 (80.0%)	60 (75.0%)	58 (72.5%)	63 (78.8%)
	Primarily THS m2.2 ([95-100]%)	47 (58.8%)	47 (58.8%)	51 (63.8%)	46 (57.5%)
	Exclusively THS m2.2 (100%)	34 (42.5%)	38 (47.5%)	44 (55.0%)	27 (33.8%)
	Predominantly THS m2.2 ([70-95]%)	17 (21.3%)	13 (16.3%)	7 (8.8%)	17 (21.3%)
	<b>Dual ([30-70]%)</b>	11 (13.8%)	12 (15.0%)	12 (15.0%)	10 (12.5%)
	Dual mostly THS m2.2 ([60-70]%)	3 (3.8%)	2 (2.5%)	3 (3.8%)	1 (1.3%)
	Dual balanced ([40-60]%)	7 (8.8%)	6 (7.5%)	5 (6.3%)	7 (8.8%)
	Dual mostly CC ([30-40]%)	1 (1.3%)	4 (5.0%)	4 (5.0%)	2 (2.5%)
	<b>CC ([0-30]%)</b>	5 (6.3%)	6 (7.5%)	5 (6.3%)	3 (3.8%)
	Predominantly CC ([5-30]%)	4 (5.0%)	5 (6.3%)	2 (2.5%)	2 (2.5%)
	Primarily CC ([0-5]%)	1 (1.3%)	1 (1.3%)	3 (3.8%)	1 (1.3%)
	Exclusively CC (0%)	0	0	2 (2.5%)	0
	Abstinent	0	0	1 (1.3%)	0
	Predominantly Abstinent	0	0	0	0
	Not Abstinent	0	1 (1.3%)	0	0
	Discontinued in previous period	0	1 (1.3%)	4 (5.0%)	4 (5.0%)



**Table 41 Summary of Product Use by Product Use Category in Ambulatory Period – FAS (continued)**

Study Arm	Product Use Categorization	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)	Ambulatory n (%)
<b>mCC Arm (N=41)</b>	CC Only (Exclusively CC)	40 (97.6%)	39 (95.1%)	36 (87.8%)	36 (87.8%)
	CC Dual (Use of other products)	0	1 (2.4%)	1 (2.4%)	1 (2.4%)
	Discontinued in previous period	1 (2.4%)	1 (2.4%)	4 (9.8%)	4 (9.8%)
<b>SA Arm (N=39)</b>	Abstinent	8 (20.5%)	7 (17.9%)	9 (23.1%)	6 (15.4%)
	Predominantly Abstinent	4 (10.3%)	5 (12.8%)	2 (5.1%)	2 (5.1%)
	Not Abstinent	22 (56.4%)	21 (53.8%)	22 (56.4%)	25 (64.1%)
	Discontinued in previous period	5 (12.8%)	6 (15.4%)	6 (15.4%)	6 (15.4%)

Abbreviations: CC = conventional cigarette; FAS = Full Analysis Set; mCC = Menthol conventional cigarette; N = number of subjects in the FAS for each arm; n = number of subjects; SA = smoking abstinence; 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]).

Percentage refers to the total number of subjects per arm.

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 endpoint variables of the primary analysis 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 endpoint variable of the primary analysis for this study in an ambulatory setting was Total NNAL urinary concentration adjusted for creatinine (pg/mg creat) in 24-hour urine 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 we have only presented data of the PP Set for the primary analysis in the Confinement Period in the CSR.

To assist with the interpretation, the profiles of the endpoints of primary analysis 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 11.2.2](#).

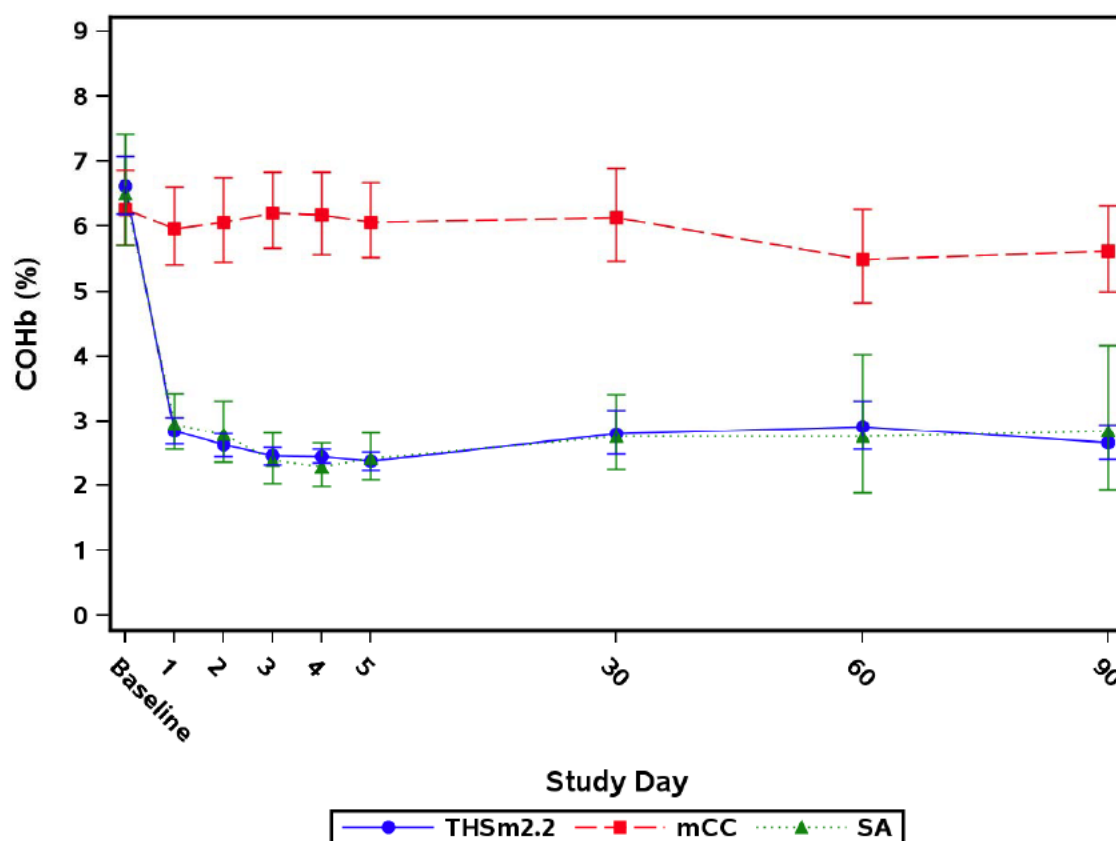
#### 11.1.1 Carboxyhemoglobin in Whole Blood (% of Saturation of Hemoglobin) on Day 5 (Confinement Period)

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 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, Compliant Population, and 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 was the last assessment prior to first 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#).

[Table 42](#) presents the results of the COHb assessments at each time point in the Confinement Period by study arm.

**Table 42 COHb in Whole Blood (%) Assessments by Study Arm During the Confinement Period (PP Set)**

Study Arm	Visit	Number of Geometric CV*		Min	Median	Max
		Subjects	Mean (%)			
THS m2.2	Baseline	74	6.66	29.163	2.2	12.6
	Day 1	74	2.84	31.339	1.8	10.8
	Day 2	74	2.62	29.207	1.6	10.8
	Day 3	74	2.46	23.229	1.4	5.9
	Day 4	74	2.44	18.040	1.5	5.9
	Day 5, 15 min < T <sub>0</sub>	67	2.38	16.932	1.5	4.9
	Day 5, 12:00-01:30 PM	65	2.49	14.337	1.7	3.8
	Day 5, 04:00-05:30 PM	66	2.39	18.884	1.4	5.2
	<b>Day 5, 08:00-09:30 PM</b>	<b>74</b>	<b>2.37</b>	<b>24.420</b>	<b>0.8</b>	<b>5.9</b>
mCC	Baseline	34	6.16	28.377	2.8	9.7
	Day 1	34	5.97	28.944	2.3	9.1
	Day 2	34	6.07	31.089	2.3	10.6
	Day 3	34	6.21	27.183	2.8	10.8
	Day 4	34	6.17	29.632	2.6	9.2
	Day 5, 15 min < T <sub>0</sub>	31	4.22	23.001	2.5	6.7
	Day 5, 12:00-01:30 PM	30	5.86	30.041	2.6	9.3
	Day 5, 04:00-05:30 PM	29	6.14	25.378	3.5	9.3
	<b>Day 5, 08:00-09:30 PM</b>	<b>34</b>	<b>6.07</b>	<b>27.534</b>	<b>2.8</b>	<b>9.7</b>
SA	Baseline	23	6.54	28.455	3.4	9.5
	Day 1	23	2.95	34.371	1.8	8.1
	Day 2	23	2.79	40.447	1.5	8.1
	Day 3	23	2.39	38.557	1.3	8.1
	Day 4	23	2.29	34.377	1.5	8.1
	Day 5, 08:00-09:30 AM	21	2.22	20.780	1.5	3.1
	Day 5, 12:00-01:30 PM	19	2.32	15.470	1.6	3.0
	Day 5, 04:00-05:30 PM	18	2.22	12.984	1.7	2.7
	<b>Day 5, 08:00-09:30 PM</b>	<b>23</b>	<b>2.42</b>	<b>35.466</b>	<b>1.6</b>	<b>8.1</b>

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 43](#) presents overall percent change from baseline in COHb at each time point in the Confinement Period by study arm.

**Table 43 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	74	-54.09	20.921	-78.6	-61.38	0.0
	Day 2	74	-57.54	19.109	-84.1	-63.43	0.0
	Day 3	74	-60.86	15.839	-78.2	-63.98	9.1
	Day 4	74	-61.09	15.228	-81.0	-63.75	4.5
	Day 5, 15 min < T <sub>0</sub>	67	-61.94	13.114	-82.6	-64.41	-9.1
	Day 5, 12:00-01:30 PM	65	-60.48	14.013	-81.7	-63.24	9.1
	Day 5, 04:00-05:30 PM	66	-61.90	13.755	-83.7	-63.96	4.5
	<b>Day 5, 08:00-09:30 PM</b>	<b>74</b>	<b>-61.67</b>	<b>16.578</b>	<b>-89.7</b>	<b>-65.17</b>	<b>0.0</b>
mCC	Day 1	34	-2.50	11.599	-20.7	-2.56	33.8
	Day 2	34	0.19	20.508	-25.0	-4.14	62.7
	Day 3	34	2.39	18.251	-32.2	0.00	37.3
	Day 4	34	0.84	12.736	-23.2	0.00	33.9
	Day 5, 15 min < T <sub>0</sub>	31	-31.92	12.304	-52.2	-33.33	-5.9
	Day 5, 12:00-01:30 PM	30	-5.45	15.869	-39.7	-6.01	36.8
	Day 5, 04:00-05:30 PM	29	-2.88	16.064	-40.3	-6.06	36.8
	<b>Day 5, 08:00-09:30 PM</b>	<b>34</b>	<b>-0.55</b>	<b>14.128</b>	<b>-21.1</b>	<b>-1.28</b>	<b>44.9</b>
SA	Day 1	23	-51.09	22.557	-72.8	-56.00	0.0
	Day 2	23	-53.09	23.402	-74.7	-57.41	0.0
	Day 3	23	-60.75	18.952	-75.3	-66.04	0.0
	Day 4	23	-62.37	18.050	-76.8	-67.95	0.0
	Day 5, 08:00-09:30 AM	21	-64.09	13.636	-77.9	-67.37	-16.7
	Day 5, 12:00-01:30 PM	19	-62.57	12.598	-79.2	-65.85	-27.8
	Day 5, 04:00-05:30 PM	18	-66.26	8.202	-76.8	-68.00	-44.1
	<b>Day 5, 08:00-09:30 PM</b>	<b>23</b>	<b>-60.02</b>	<b>19.127</b>	<b>-75.8</b>	<b>-66.67</b>	<b>0.0</b>

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 and a further decrease observed on Day 2, before plateauing during the Confinement Period.

Geometric mean COHb values decreased in the THS 2.2 Menthol arm from baseline (6.66%) to Day 5 (2.37%) in contrast to COHb values in the mCC arm, which remained similar at baseline (6.16%) and the evening measurement on Day 5 (6.07%). These values



corresponded to percent changes from baseline of -61.67% and -0.55% 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 (-54.09%). In the SA arm, geometric mean COHb values decreased from baseline (6.54%) to Day 5 (2.42%), as expected, which corresponded to a -60.02% 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, mean COHb levels in blood were higher in all study arms for subjects who smoked >19 cigarettes/day compared to subjects who smoked 10 to 19 cigarettes/day, with means of 6.53% to 7.26% and 5.92% to 6.24%, respectively. On Day 5 (08:00 to 09:30 PM) in the THS 2.2 Menthol arm, the mean percentage decrease from baseline was greater in subjects who smoked >19 cigarettes/day compared to those who smoked 10 to 19 cigarettes/day, with mean decreases of -67.27 (95% CI: -72.81, -61.73) and -57.39% (95% CI: -62.50, -52.29), respectively. Decreases from baseline to Day 5 in the mCC and SA arms were comparable between subjects who smoked 10 to 19 and >19 cigarettes/day.

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 44](#).

**Table 44 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	74	2.33	38.14		26.50	34.24, 42.47	< .001
mCC	34	6.11					

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/CC 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 61.86% lower than that of subjects who continued to smoke mCC (95% CI: 57.53, 65.76; 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 being 62.94% lower than that of subjects who continued to smoke mCC (95% CI: 59.18, 66.36; 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 (61.86% reduction).

#### 11.1.2 Monohydroxybutenyl Mercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 5 (Confinement Period)

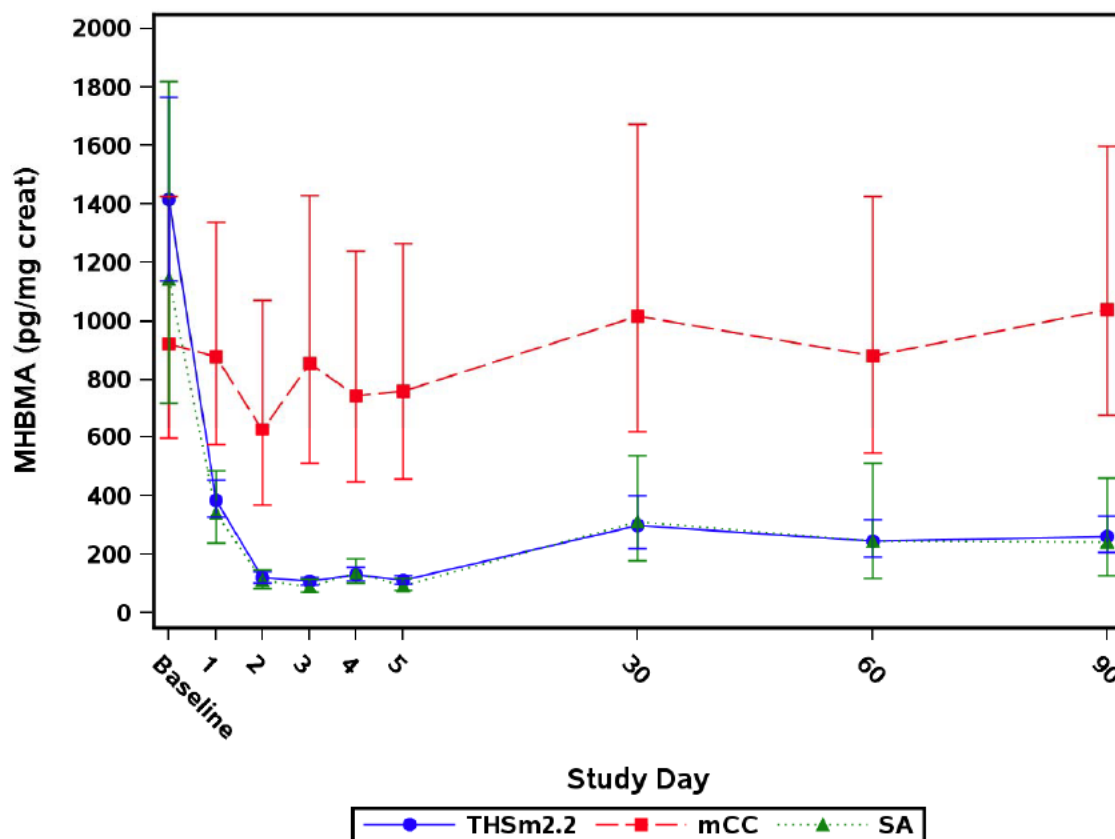
Subject listings of MHBMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

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; MHMBA = monohydroxybutenyl mercapturic acid; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was the last assessment prior to first 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#).

[Table 45](#) presents the results of the MHBMA concentrations adjusted for creatinine in the Confinement Period by study arm.

**Table 45 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			Min	Median	Max
		Subjects	Mean	CV* (%)			
THS m2.2	Baseline	65	1416.94	109.332	155.7	1434.51	10792.9
	Day 1	71	385.21	78.638	104.6	369.49	4505.1
	Day 2	71	120.03	70.380	29.1	136.25	460.5
	Day 3	71	107.39	57.153	33.3	104.17	396.2
	Day 4	71	130.57	88.338	23.0	136.60	1168.4
	Day 5	71	113.01	60.404	23.6	116.55	686.5
mCC	Baseline	30	922.66	170.171	96.3	1459.42	5519.7
	Day 1	33	877.17	176.153	75.0	1525.50	3297.0
	Day 2	33	629.39	292.537	23.6	1120.85	4601.5
	Day 3	33	855.56	268.299	56.1	1651.82	5332.6
	Day 4	33	745.66	260.880	49.5	1385.07	4308.3
	Day 5	33	760.36	261.147	43.5	1401.87	4975.4
SA	Baseline	21	1145.57	134.630	125.0	1634.33	5922.7
	Day 1	22	339.98	95.178	57.1	418.21	1368.4
	Day 2	22	111.83	70.471	46.3	99.59	310.9
	Day 3	22	90.01	58.160	45.5	87.50	253.2
	Day 4	22	137.12	73.671	42.4	136.41	465.7
	Day 5	22	93.99	52.409	45.0	94.32	200.0

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 46](#) presents overall percent change from baseline in MHBMA concentration adjusted for creatinine in the Confinement Period by study arm.



**Table 46 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					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 1	65	-67.76	22.079	-89.9	-75.37	8.3
	Day 2	65	-86.27	20.852	-98.8	-92.16	58.0
	Day 3	65	-89.67	11.142	-98.8	-92.66	-19.9
	Day 4	65	-83.65	23.588	-99.2	-91.40	57.0
	Day 5	65	-87.52	14.545	-98.8	-92.50	-10.1
mCC	Day 1	30	6.82	59.654	-51.2	-10.94	178.8
	Day 2	30	-9.08	71.967	-88.9	-20.08	302.0
	Day 3	30	8.07	67.346	-86.9	-12.04	270.1
	Day 4	30	2.07	68.094	-79.0	-9.93	256.8
	Day 5	30	2.27	77.542	-67.6	-16.84	334.7
SA	Day 1	21	-66.45	24.602	-88.4	-74.52	29.4
	Day 2	21	-84.09	19.397	-97.6	-93.10	-16.2
	Day 3	21	-81.87	30.268	-98.2	-94.87	19.8
	Day 4	21	-73.16	43.762	-96.9	-91.45	53.8
	Day 5	21	-82.14	32.744	-98.2	-94.93	46.0

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 (1416.94 pg/mg creat) to Day 5 (113.01 pg/mg creat) in contrast to MHBMA values in the mCC arm, where only a small decrease from baseline (922.66 pg/mg creat) to Day 5 (760.36 pg/mg creat) was observed. Maximum percent changes from baseline on Day 5 of -87.52% and 2.27% were observed 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 (86.27%). In the SA arm, geometric mean MHBMA values decreased from baseline (1145.57 pg/mg creat) to Day 5 (93.99 pg/mg creat), as expected, which corresponded to a -82.14% change from baseline, with the majority of the decrease observed by Day 2.



At baseline and throughout the Confinement Period, mean levels of MHBMA were higher in females compared to males for all study arms although the percent changes from baseline were comparable between genders. In the THS 2.2 Menthol and SA arms, levels of MHBMA were higher at baseline in subjects who smoked >19 cigarettes/day compared to those who smoked 10 to 19 cigarettes/day but were comparable by Day 2. In the mCC arm, levels of MHBMA were higher in subjects who smoked 10 to 19 cigarettes/day at baseline and throughout the Confinement Period.

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 47](#).

**Table 47 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		CV (%)	95% CI	p-value
			(THS m2.2:mCC) (%)				
THS m2.2	65	110.96	12.58		76.92	9.27, 17.05	< .001
mCC	30	882.25					

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/CC 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 87.42% lower than that of subjects who continued to smoke mCC (95% CI: 82.95, 90.73; 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 87.65% lower than that of subjects who continued to smoke mCC (95% CI: 83.17, 90.93; 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 (87.42% reduction).

The results for the quantity of MHBMA excreted over 24 hours ([Appendix 15, Table 15.2.3.4](#)) were consistent with the results of the urinary concentration adjusted for





creatinine, with the LS mean of MHBMA in subjects who switched to THS 2.2 Menthol 87.44% lower than that of subjects who continued to smoke mCC (95% CI: 82.99, 90.72; p-value <0.001).

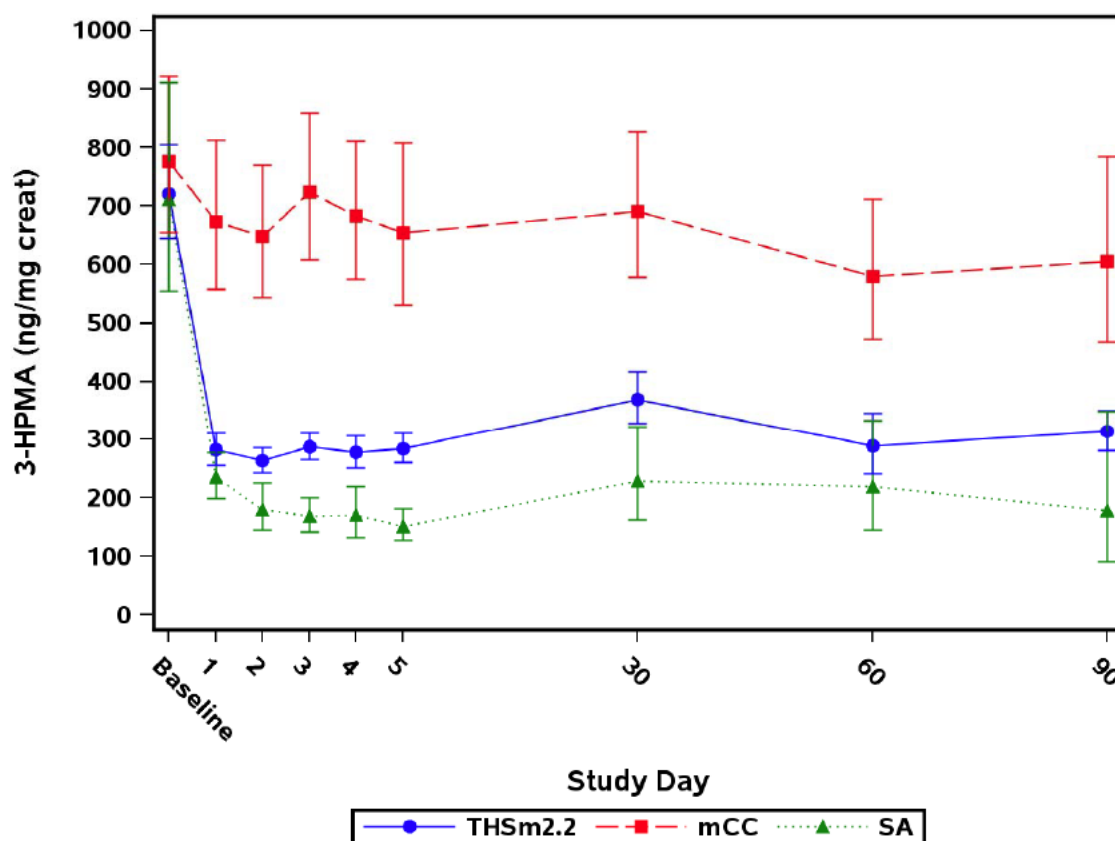
#### 11.1.3 3-hydroxypropylmercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 5 (Confinement Period)

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-hydroxypropylmercapturic acid; CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was the last assessment prior to first 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#)

[Table 48](#) presents the results of the 3-HPMA concentrations adjusted for creatinine in the Confinement Period by study arm.

**Table 48 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	67	721.15	47.744	181.0	724.29	2004.9
	Day 1	73	282.07	44.660	101.9	274.22	1459.4
	Day 2	73	263.31	35.893	134.7	268.67	548.3
	Day 3	73	286.75	36.169	106.5	280.42	615.7
	Day 4	73	276.90	44.690	88.3	279.53	755.6
	Day 5	73	283.88	39.406	95.1	263.11	730.2
mCC	Baseline	30	777.25	48.195	286.3	812.51	1838.1
	Day 1	34	673.53	57.809	185.3	701.25	1838.1
	Day 2	34	647.86	53.114	242.0	652.13	1838.1
	Day 3	34	723.58	52.443	257.8	646.89	2098.6
	Day 4	34	683.45	52.292	213.0	692.56	1838.1
	Day 5	34	655.19	66.434	105.6	686.62	1838.1
SA	Baseline	21	711.68	58.646	166.9	791.98	1942.1
	Day 1	22	234.26	39.202	78.1	247.51	443.0
	Day 2	22	180.00	53.654	44.6	173.69	378.8
	Day 3	22	168.33	41.220	48.9	170.64	303.8
	Day 4	22	169.91	62.362	28.4	171.92	494.0
	Day 5	22	151.43	42.172	56.7	152.55	295.2

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 49](#) presents overall percent change from baseline in 3-HPMA concentration adjusted for creatinine in the Confinement Period by study arm.



**Table 49 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					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 1	67	-57.96	18.693	-80.4	-63.16	13.5
	Day 2	67	-60.56	15.761	-81.9	-62.61	24.3
	Day 3	67	-57.33	19.366	-84.7	-61.28	47.9
	Day 4	67	-57.37	16.824	-80.6	-59.97	-7.9
	Day 5	67	-58.76	15.735	-80.1	-62.46	-7.3
mCC	Day 1	30	-11.74	24.140	-54.3	-14.57	30.5
	Day 2	30	-10.72	27.604	-58.8	-14.01	76.5
	Day 3	30	-4.29	24.819	-49.5	-9.94	53.9
	Day 4	30	-7.79	26.631	-72.0	-7.52	80.4
	Day 5	30	-12.91	32.845	-64.6	-9.20	110.5
SA	Day 1	21	-63.39	22.278	-84.2	-69.21	-2.9
	Day 2	21	-73.09	8.390	-86.6	-74.55	-57.6
	Day 3	21	-73.15	18.930	-88.6	-76.80	-9.0
	Day 4	21	-72.85	15.881	-93.2	-78.30	-30.1
	Day 5	21	-75.51	14.122	-93.0	-79.94	-40.6

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 was 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 (721.15 ng/mg creat) to Day 5 (283.88 ng/mg creat) whereas 3-HPMA values in the mCC arm showed a smaller decrease from baseline (777.25 ng/mg creat) to Day 5 (655.19 ng/mg creat). These values corresponded to percent changes from baseline of -58.76% and -12.91% 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 (-57.96%). In the SA arm, geometric mean 3-HPMA values decreased from baseline (711.68 ng/mg creat) to Day 5 (151.43 ng/mg creat), as expected, which corresponded to a -75.51% change from baseline, with the majority of the decrease observed by Day 1.





At baseline, mean levels of 3-HPMA were higher in females compared to males for all study arms. By Day 3, 3-HPMA levels were comparable between males and females for the THS 2.2 Menthol and SA arms; however, 3-HPMA levels were higher in females compared to males throughout the Confinement Period in the mCC arm. Percent changes from baseline were comparable for males and females for all study arms.

At baseline, mean levels of 3-HPMA were higher in subjects who smoked >19 cigarettes/day compared to subjects who smoked 10 to 19 cigarettes/day in all study arms. This trend continued until Day 3 for the THS 2.2 Menthol and SA arms, and until Day 4 for the mCC arm when levels became comparable between high and low smokers.

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 50](#).

**Table 50 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		CV (%)	95% CI	p-value
			(THS m2.2:mCC) (%)				
THS m2.2	67	278.13	45.77		36.45	39.22, 53.41	< .001
mCC	30	607.68					

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 54.23% lower than that of subjects who continued to smoke mCC (95% CI: 46.59, 60.78; 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 53.38% lower than that of subjects who continued to smoke mCC (95% CI: 45.53, 60.10; 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 (54.23% reduction).



The results for the quantity of 3-HPMA excreted over 24 hours ([Appendix 15, Table 15.2.3.4](#)) were consistent with the results of the urinary concentration adjusted for creatinine, with the LS mean of 3-HPMA in subjects who switched to THS 2.2 Menthol 54.86% lower than that of subjects who continued to smoke mCC (95% CI: 46.83, 61.67; p-value <0.001).

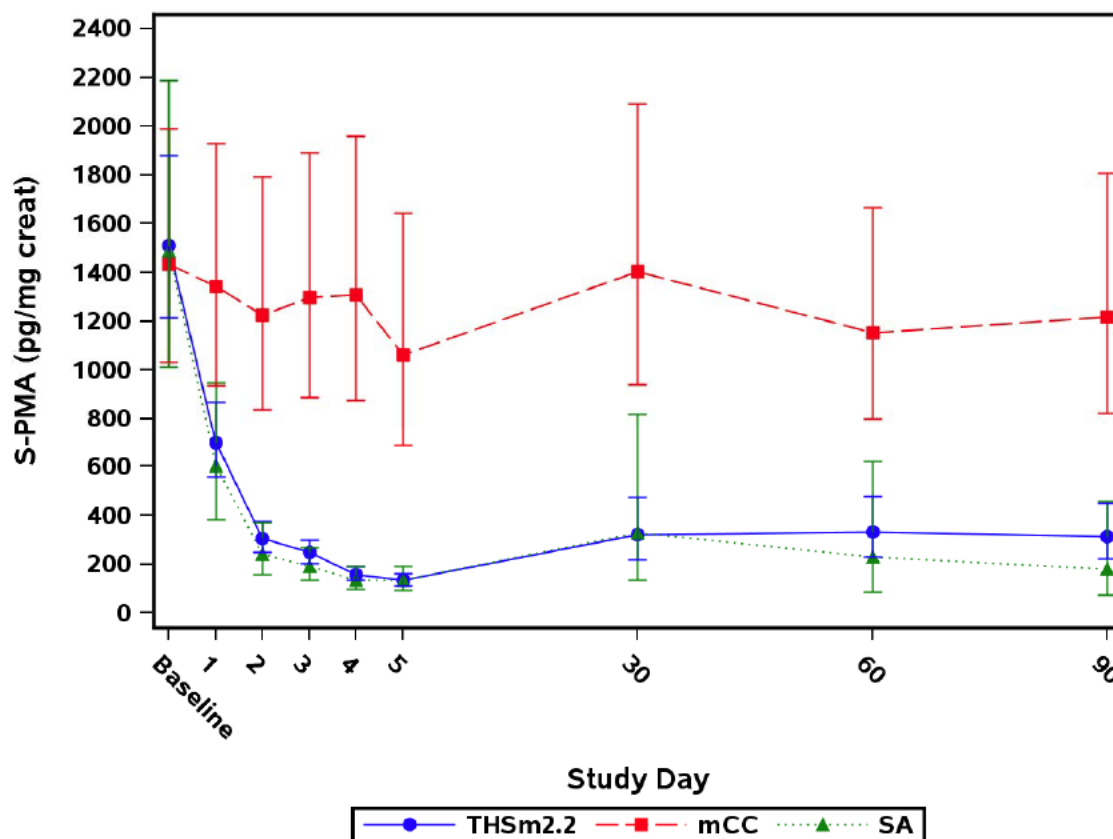
#### 11.1.4 S-phenylmercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 5 (Confinement Period)

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, the Compliant Population, and 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; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#).

[Table 51](#) presents the results of the S-PMA concentrations adjusted for creatinine in the Confinement Period by study arm.

**Table 51 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			Min	Median	Max
		Subjects	Mean	CV* (%)			
THS m2.2	Baseline	65	1510.14	108.680	93.0	1776.79	9243.9
	Day 1	71	694.93	119.599	47.2	802.61	6220.9
	Day 2	71	304.41	102.054	32.2	292.52	2512.8
	Day 3	71	246.31	95.700	24.5	240.52	4261.7
	Day 4	71	158.45	88.790	27.1	142.73	954.9
	Day 5	71	133.64	86.656	18.7	131.05	1269.2
mCC	Baseline	30	1433.17	107.941	160.8	1486.69	4946.2
	Day 1	33	1344.34	134.554	91.3	1472.30	6110.2
	Day 2	33	1224.38	147.838	117.8	1347.42	5703.9
	Day 3	33	1295.86	145.108	118.4	1701.39	7010.7
	Day 4	33	1307.80	162.607	50.1	1790.54	5475.4
	Day 5	33	1062.05	189.124	118.7	1557.46	6677.6
SA	Baseline	21	1488.78	102.283	213.5	1624.50	8015.0
	Day 1	22	602.09	136.564	58.3	704.52	4532.2
	Day 2	22	241.86	121.679	25.9	243.33	2178.2
	Day 3	22	190.44	89.125	37.4	174.79	1492.7
	Day 4	22	135.71	87.885	32.8	120.55	944.4
	Day 5	22	133.11	99.339	20.9	123.18	1008.6

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 52](#) presents overall percent change from baseline in S-PMA concentration adjusted for creatinine data in the Confinement Period by study arm.





**Table 52 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					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 1	65	-48.31	31.687	-83.2	-52.46	129.5
	Day 2	65	-75.51	19.333	-94.5	-79.49	36.9
	Day 3	65	-75.83	46.457	-95.4	-85.01	276.4
	Day 4	65	-86.72	11.765	-97.8	-90.00	-21.4
	Day 5	65	-88.81	8.745	-98.5	-91.16	-57.6
mCC	Day 1	30	6.02	39.252	-62.2	3.85	101.1
	Day 2	30	3.10	54.959	-75.5	-2.77	150.8
	Day 3	30	7.91	56.392	-92.3	-3.97	147.0
	Day 4	30	6.15	49.555	-94.4	-1.87	142.7
	Day 5	30	-12.55	42.740	-91.2	-0.64	71.6
SA	Day 1	21	-55.52	20.790	-92.8	-53.20	-12.2
	Day 2	21	-81.70	7.728	-94.5	-83.45	-68.2
	Day 3	21	-85.29	11.399	-96.8	-87.43	-40.1
	Day 4	21	-89.59	6.213	-96.7	-91.62	-71.0
	Day 5	21	-89.87	6.267	-97.2	-91.74	-70.7

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 was 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 (1510.14 pg/mg creat) to Day 5 (133.64 pg/mg creat), whereas S-PMA values in the mCC arm showed a smaller decrease from baseline (1433.17 pg/mg creat) to Day 5 (1062.05 pg/mg creat). These values correspond to percent changes from baseline of -88.81% and -12.55% 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 (1488.78 pg/mg creat) to Day 5 (133.11 pg/mg creat), as expected, which corresponded to a -89.87% change from baseline, with the majority of the decrease achieved by Day 1.



At baseline and throughout the Confinement Period, mean levels of S-PMA were higher in females compared to males for all study arms.

Levels of S-PMA were higher in subjects who smoked >19 cigarettes/day compared to subjects who smoked 10 to 19 cigarettes/day in the THS 2.2 Menthol and SA arms at baseline until Day 5. In the mCC arm, levels of S-PMA were higher at baseline in subjects who smoked 10 to 19 cigarettes/day compared to subjects who smoked >19 cigarettes/day; however, values were comparable between high and low smokers on most study days in the Confinement Period.

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 53](#).

**Table 53 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		CV (%)	95% CI	p-value
			Ratio	(THS m2.2:mCC) (%)			
THS m2.2	65	134.11					
mCC	30	1065.91	12.58		69.68	9.54, 16.58	< .001

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 87.42% lower than that of subjects who continued to smoke mCC (95% CI: 83.42, 90.46; 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 87.40% lower than that of subjects who continued to smoke mCC (95% CI: 83.30, 90.50; 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 (87.42% reduction).



The results for the quantity of S-PMA excreted over 24 hours ([Appendix 15, Table 15.2.3.4](#)) were consistent with the results of the urinary concentration adjusted for creatinine, with the LS mean of S-PMA in subjects who switched to THS 2.2 Menthol 87.38% lower than that of subjects who continued to smoke mCC (95% CI: 83.28, 90.48; p-value <0.001).

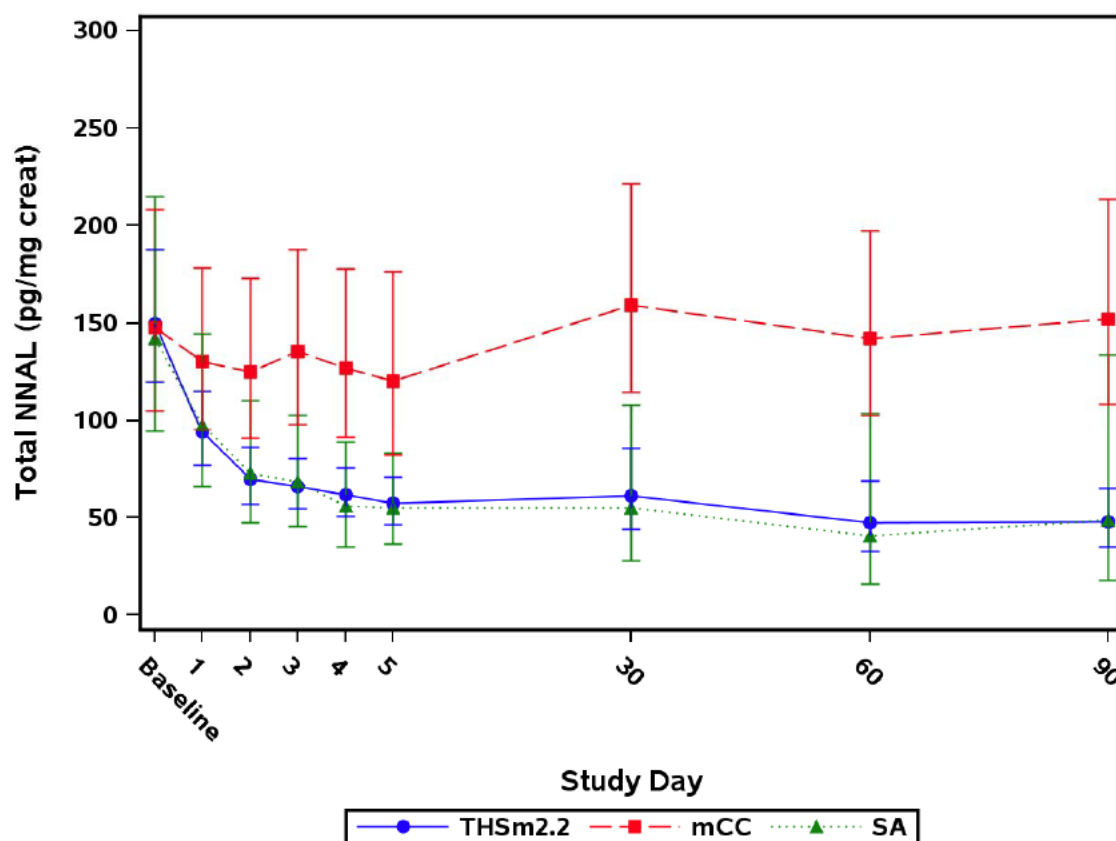
#### 11.1.5 Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in 24-hour Urine (Concentration Adjusted for Creatinine) on Day 90 (Ambulatory Period)

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, the Compliant Population, and FAS, respectively. Data for PP Set was also 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; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#).

[Table 54](#) presents the results of the Total NNAL concentrations adjusted for creatinine following the Ambulatory Period by study arm.





**Table 54 Absolute Values of Total NNAL Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm (Ambulatory Period) (PP Set)**

Study Arm	Visit	Number of Geometric			Min	Median	Max
		Subjects	Mean	CV* (%)			
THS m2.2	Baseline	67	150.01	115.699	5.0	187.11	643.9
	Day 5	73	57.04	112.782	1.2	68.40	240.5
	Day 30	40	60.99	141.182	1.6	58.37	740.2
	Day 60	39	47.11	169.294	1.8	45.79	671.6
	Day 90	47	47.53	144.336	2.3	47.37	474.7
mCC	Baseline	30	147.90	115.044	15.3	136.01	1154.7
	Day 5	34	120.29	152.188	6.1	107.18	1154.7
	Day 30	33	159.55	116.857	23.8	164.46	1158.1
	Day 60	34	142.45	118.187	25.3	157.27	581.8
	Day 90	32	152.11	119.154	20.8	164.09	542.9
SA	Baseline	21	142.18	112.752	35.3	118.29	979.6
	Day 5	22	54.74	118.058	11.9	53.99	392.4
	Day 30	13	54.96	158.452	7.2	52.26	381.5
	Day 60	11	40.39	247.326	3.6	55.60	339.4
	Day 90	9	48.63	215.553	2.9	71.19	235.3

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 55](#) presents overall percent change from baseline in Total NNAL concentration adjusted for creatinine data.



**Table 55 Percent Change from Baseline Total NNAL Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm (Ambulatory Period) (PP Set)**

Study Arm	Visit	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 5	67	-60.23	14.023	-84.5	-60.03	16.3
	Day 30	37	-51.95	32.944	-90.7	-65.26	46.5
	Day 60	35	-61.26	29.043	-90.4	-70.58	14.2
	<b>Day 90</b>	<b>43</b>	<b>-56.45</b>	<b>40.351</b>	<b>-93.9</b>	<b>-67.08</b>	<b>83.3</b>
mCC	Day 5	30	-5.58	38.839	-81.8	-5.20	114.0
	Day 30	29	42.80	67.393	-57.6	27.32	238.8
	Day 60	30	24.47	58.456	-53.7	5.33	177.9
	<b>Day 90</b>	<b>29</b>	<b>32.30</b>	<b>67.070</b>	<b>-58.7</b>	<b>24.87</b>	<b>177.9</b>
SA	Day 5	21	-58.86	17.834	-85.0	-61.45	-11.1
	Day 30	12	-55.86	26.355	-90.3	-55.88	-2.9
	Day 60	11	-45.20	33.784	-97.8	-38.34	-5.2
	<b>Day 90</b>	<b>9</b>	<b>-1.97</b>	<b>116.928</b>	<b>-98.2</b>	<b>-34.62</b>	<b>286.9</b>

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 was 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 0 to Day 90.

Geometric mean Total NNAL values decreased in the THS 2.2 Menthol arm from baseline (150.01 pg/mg creat) to Day 90 (47.53 pg/mg creat), whereas Total NNAL values in the mCC arm was comparable to baseline (147.90 pg/mg creat) on Day 90 (152.11 pg/mg creat). These values corresponded to percent changes from baseline of -56.45% and 32.30% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total NNAL values decreased from baseline (142.18 pg/mg creat) to Day 90 (48.63 pg/mg creat), as expected. The mean change from baseline to Day 90 for the SA arm was only -1.97% as the value appears to be skewed by outliers and the limited number of subjects in the PP Set for the SA arm on Day 90 (N=9). As a consequence, the median value of -34.62% is a more reliable estimate.

At baseline, mean levels of Total NNAL were higher in females compared to males in the THS 2.2 Menthol and mCC arms. On Day 90, levels of Total NNAL remained higher in females than males in the mCC arm and were comparable in the THS 2.2 Menthol arm.



There were only 2 female subjects in the PP Set for the SA arm on Day 90, therefore comparison to male subjects is difficult and the results should be interpreted with caution.

At baseline and Day 90, mean levels of Total NNAL were higher in subjects who smoked >19 cigarettes/day compared to subjects who smoked 10 to 19 cigarettes/day in the THS 2.2 Menthol arm and comparable in the mCC arm. Comparison between low and high smokers is difficult in the SA arm due to the limited number of subjects in the PP Set on Day 90.

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 56](#).

**Table 56 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	43	41.05	26.41		106.00	17.31, 40.26	< .001
mCC	29	155.45					
Compliant Population							
THS m2.2	37	42.84	28.10		110.39	17.89, 44.13	< .001
mCC	29	152.46					

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. P-value on Day 90 is evaluated only if p-value on Day 5 is significant, in all biomarkers except for Total NNAL.

Total NNAL was evaluated on Day 90 while the other biomarkers were evaluated on Day 5.

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 73.59% lower than that of subjects who continued to smoke mCC (95% CI: 59.74, 82.69; p-value <0.001) within the PP Set.

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 Total NNAL in subjects





who switched to THS 2.2 Menthol 72.70% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 58.20, 82.17; p-value <0.001). In addition, analysis of Total NNAL on Day 90 on the Compliant Population was consistent with the results on the PP Set, with the LS mean of Total NNAL in subjects who switched to THS 2.2 Menthol use 71.90% lower than that of subjects who continued to smoke mCC (95% CI: 55.87, 82.11; 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 (73.59% reduction) on Day 90.

The results for the quantity of Total NNAL excreted over 24 hours ([Appendix 15, Table 15.2.3.4](#)) on Day 90 were consistent with the results of the urinary concentration adjusted for creatinine for the PP Set, with the LS mean of Total NNAL in subjects who switched to THS 2.2 Menthol 73.01% lower than that of subjects who continued to smoke mCC (95% CI: 58.34, 82.52; p-value <0.001).

## 11.2 Analysis of Secondary Objectives/Endpoints

All endpoint variables for this study were studied in a confinement setting and 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 analyses of primary biomarker assessments, not yet discussed as part of the primary objective ([Section 11.1](#)), are presented in [Section 11.2.1](#) (COHb, MHBMA, 3-HPMA, S-PMA on Day 90, and Total NNAL on Day 5) and in [Section 11.2.2](#) (analysis of primary biomarkers versus SA).

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 BoExps, the statistical analysis on the PP Set was repeated with a mixed model approach. In addition, as a further sensitivity analysis for the BoExps, 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.

### 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 evening 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 57](#) presents the results of the COHb assessments at each time point in the Ambulatory Period by study arm.

**Table 57 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	74	6.66	29.163	2.2	6.85	12.6
	Day 5	74	2.37	24.420	0.8	2.40	5.9
	Day 30	40	2.80	38.803	1.5	2.70	7.3
	Day 60	39	2.91	41.628	1.7	2.70	9.2
	Day 90	47	2.66	35.163	1.6	2.50	6.4
mCC	Baseline	34	6.16	28.377	2.8	6.25	9.7
	Day 5	34	6.07	27.534	2.8	6.25	9.7
	Day 30	34	6.13	34.149	2.4	6.15	10.6
	Day 60	35	5.49	39.299	2.4	6.20	12.7
	Day 90	32	5.62	33.240	2.4	5.60	10.3
SA	Baseline	23	6.54	28.455	3.4	6.80	9.5
	Day 5	23	2.42	35.466	1.6	2.20	8.1
	Day 30	13	2.76	35.472	1.7	2.40	5.6
	Day 60	12	2.76	64.752	1.5	2.05	7.7
	Day 90	9	2.84	52.689	1.5	2.50	7.7

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.

Data Source: [Appendix 15](#), [Table 15.2.4.1.1](#).

[Table 58](#) presents overall percent change from baseline in COHb evening assessment data in the Ambulatory Period by study arm.

**Table 58 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, 08:00-09:30 PM	74	-61.67	16.578	-89.7	-65.17	0.0
	Day 30	40	-49.97	27.201	-83.3	-54.36	22.7
	Day 60	39	-48.85	28.336	-84.1	-56.60	36.4
	<b>Day 90</b>	<b>47</b>	<b>-55.30</b>	<b>21.368</b>	<b>-84.9</b>	<b>-57.97</b>	<b>45.5</b>
mCC	Day 5, 08:00-09:30 PM	34	-0.55	14.128	-21.1	-1.28	44.9
	Day 30	34	0.97	22.635	-31.8	0.00	71.0
	Day 60	35	-7.23	25.912	-64.2	-4.17	54.9
	<b>Day 90</b>	<b>32</b>	<b>-6.88</b>	<b>22.143</b>	<b>-64.2</b>	<b>-7.15</b>	<b>37.3</b>
SA	Day 5, 08:00-09:30 PM	23	-60.02	19.127	-75.8	-66.67	0.0
	Day 30	13	-50.99	36.353	-75.0	-57.41	64.7
	Day 60	12	-37.75	58.749	-78.3	-57.84	126.5
	<b>Day 90</b>	<b>9</b>	<b>-35.24</b>	<b>64.000</b>	<b>-77.9</b>	<b>-53.70</b>	<b>126.5</b>

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 evening COHb in the THS 2.2 Menthol arm was comparable to that of the SA arm ([Figure 4](#)). Geometric mean COHb values during the Ambulatory Period in the THS 2.2 Menthol arm remained decreased from baseline (6.66%) and similar to Day 5 (2.37%), with values on Days 30, 60, and 90 of 2.80%, 2.91%, and 2.66%, respectively. In contrast, in the mCC arm COHb values were comparable to baseline (6.16%) on Days 30, 60, and 90, with values of 6.13%, 5.49%, and 5.62%, respectively. These values corresponded to percent changes from baseline on Day 90 of -55.30% and -6.88% 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 (6.54%) and comparable to Day 5 (2.42%), as expected, with values on Days 30, 60, and 90 of 2.76%, 2.76%, and 2.84%, respectively, corresponding to percent changes from baseline of -50.99%, -37.75%, and -35.24%, respectively.

Analysis of evening blood COHb (%) for THS 2.2 Menthol users versus mCC use on Day 90 is presented in [Appendix 15, Table 15.2.3.2](#) for the PP Set and in [Table 15.2.3.3](#) 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 59](#).

**Table 59 Analysis of Evening Blood COHb (%) versus mCC on Day 90 (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	47	2.65	46.76		36.30	39.75, 55.00	< .001
mCC	32	5.66					

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 15.2.3.2](#).

On Day 90, the LS mean of COHb in subjects who switched to THS 2.2 Menthol use was 53.24% lower than that of subjects who continued to smoke mCC (95% CI: 45.00, 60.25; p-value <0.001).

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.6](#)), with the LS mean of COHb in subjects who switched to THS 2.2 Menthol being 56.72% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 49.08, 63.21; 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 COHb in subjects who switched to THS 2.2 Menthol being 54.55% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 47.14, 60.76; 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 FAS, respectively. Data for the PP Set are also provided in [Figure 5](#).

[Table 60](#) presents the results of the MHBMA concentrations adjusted for creatinine at each time point in the Ambulatory Period by study arm.

**Table 60 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			Min	Median	Max
		Subjects	Mean	CV (%)			
THS m2.2	Baseline	65	1416.94	109.332	155.7	1434.51	10792.9
	Day 5	71	113.01	60.404	23.6	116.55	686.5
	Day 30	39	297.29	114.408	53.9	292.35	2041.6
	Day 60	39	245.94	93.944	41.3	249.39	1133.8
	Day 90	47	260.98	97.527	62.3	261.18	1359.2
mCC	Baseline	30	922.66	170.171	96.3	1459.42	5519.7
	Day 5	33	760.36	261.147	43.5	1401.87	4975.4
	Day 30	32	1017.53	239.489	31.4	2073.52	4646.6
	Day 60	33	882.02	229.819	28.2	1294.12	5838.9
	Day 90	32	1040.71	176.488	55.4	1709.96	6715.6
SA	Baseline	21	1145.57	134.630	125.0	1634.33	5922.7
	Day 5	22	93.99	52.409	45.0	94.32	200.0
	Day 30	13	310.59	113.194	53.2	322.28	1012.9
	Day 60	11	244.33	152.040	52.4	260.71	1676.8
	Day 90	9	243.00	100.030	60.2	266.20	1141.2

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 61](#) presents overall percent change from baseline in MHBMA concentration adjusted for creatinine in the Ambulatory Period by study arm.



**Table 61 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					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 5	65	-87.52	14.545	-98.8	-92.50	-10.1
	Day 30	36	-66.02	33.577	-98.5	-76.16	22.9
	Day 60	35	-72.24	31.526	-98.0	-84.59	28.9
	<b>Day 90</b>	<b>43</b>	<b>-73.29</b>	<b>29.678</b>	<b>-97.8</b>	<b>-84.74</b>	<b>68.3</b>
mCC	Day 5	30	2.27	77.542	-67.7	-16.84	334.7
	Day 30	29	26.74	62.723	-82.3	19.39	172.7
	Day 60	30	12.13	69.468	-59.6	-12.26	208.8
	<b>Day 90</b>	<b>29</b>	<b>36.09</b>	<b>97.847</b>	<b>-50.9</b>	<b>-1.63</b>	<b>324.0</b>
SA	Day 5	21	-82.14	32.744	-98.2	-94.93	46.0
	Day 30	12	-39.18	73.569	-95.5	-83.56	116.1
	Day 60	11	-29.15	86.362	-96.0	-54.51	189.2
	<b>Day 90</b>	<b>9</b>	<b>-27.04</b>	<b>74.186</b>	<b>-89.2</b>	<b>-79.84</b>	<b>96.8</b>

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 was 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 during the Ambulatory Period in the THS 2.2 Menthol arm remained decreased from baseline (1416.94 pg/mg creat) but higher than Day 5 (113.01 pg/mg creat), with values on Days 30, 60, and 90 of 297.29, 245.94, and 260.98 pg/mg creat, respectively. In the mCC arm, MHBMA was comparable to baseline (922.66 pg/mg creat) on Days 30, 60, and 90, with values of 1017.53, 882.02, and 1040.71 pg/mg creat, respectively. These values corresponded to percent changes from baseline on Day 90 of -73.29% and 36.09% 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 (1145.57 pg/mg creat) but higher than Day 5 (93.99 pg/mg creat), with values on Days 30, 60, and 90 of 310.59, 244.33, and 243.00 pg/mg creat, respectively, corresponding to percent changes from baseline of -39.18%, -29.15%, and -27.04%, respectively. It should be noted that the number of subjects in the PP Set for the SA arm was lower in the Ambulatory Period (N = 9 to 12) compared to the Confinement Period (N = 21 to 22).



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 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 [Table 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 62](#).

**Table 62 Analysis of MHBMA versus mCC on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean Ratio Geometric (THS m2.2:mCC)			
			LS Mean	(%)	CV(%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	45	364.12	19.44	87.08	13.48, 28.03
	mCC	29	1873.19			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	213.78	18.52	85.36	12.85, 26.67
	mCC	29	1154.52			

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.

Data Source: [Appendix 15, Table 15.2.3.2](#) and [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 81.48% lower than that of subjects who continued to smoke mCC (95% CI: 73.33, 87.15; 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.

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 81.42% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 73.06, 87.19; 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 MHBMA urinary concentration adjusted for creatinine in subjects



who switched to THS 2.2 Menthol being 80.86% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 72.57, 86.65; 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 63](#) presents the results of the 3-HPMA concentrations adjusted for creatinine at each time point in the Ambulatory Period by study arm.

**Table 63 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		Geometric			
		Subjects	Mean	CV (%)	Min	Median	Max
THS m2.2	Baseline	67	721.15	47.744	181.0	724.29	2004.9
	Day 5	73	283.88	39.406	95.1	263.11	730.2
	Day 30	40	369.55	39.090	101.2	364.98	809.3
	Day 60	39	289.18	59.522	86.6	287.91	724.1
	<b>Day 90</b>	<b>47</b>	<b>314.05</b>	<b>38.577</b>	<b>115.6</b>	<b>314.85</b>	<b>744.4</b>
mCC	Baseline	30	777.25	48.195	286.3	812.51	1838.1
	Day 5	34	655.19	66.434	105.6	686.62	1838.1
	Day 30	33	691.59	54.099	343.6	637.25	2288.3
	Day 60	34	580.28	64.250	146.6	659.06	1933.2
	<b>Day 90</b>	<b>32</b>	<b>606.10</b>	<b>81.767</b>	<b>73.4</b>	<b>655.35</b>	<b>1652.8</b>
SA	Baseline	21	711.68	58.646	166.9	791.98	1942.1
	Day 5	22	151.43	42.172	56.7	152.55	295.2
	Day 30	13	228.14	62.087	84.5	232.67	497.2
	Day 60	11	219.07	68.779	67.2	244.44	572.7
	<b>Day 90</b>	<b>9</b>	<b>177.90</b>	<b>107.152</b>	<b>22.1</b>	<b>251.33</b>	<b>383.1</b>

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 64 presents overall percent change from baseline in 3-HPMA concentration adjusted for creatinine in the Ambulatory Period by study arm.

**Table 64 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					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Day 5	67	-58.76	15.735	-80.1	-62.46	-7.3
	Day 30	37	-44.76	22.465	-87.5	-48.00	0.4
	Day 60	35	-52.08	27.579	-84.7	-55.50	48.7
	<b>Day 90</b>	<b>43</b>	<b>-53.82</b>	<b>18.413</b>	<b>-89.4</b>	<b>-56.30</b>	<b>-1.6</b>
mCC	Day 5	30	-12.91	32.845	-64.6	-9.20	110.5
	Day 30	29	0.46	38.612	-56.7	-7.91	149.2
	Day 60	30	-13.08	35.023	-53.5	-19.50	105.7
	<b>Day 90</b>	<b>29</b>	<b>-5.54</b>	<b>48.286</b>	<b>-81.3</b>	<b>-8.55</b>	<b>168.9</b>
SA	Day 5	21	-75.51	14.122	-93.0	-79.94	-40.6
	Day 30	12	-63.88	16.600	-86.1	-63.30	-37.1
	Day 60	11	-57.26	24.159	-84.6	-62.10	1.9
	<b>Day 90</b>	<b>9</b>	<b>-57.21</b>	<b>31.129</b>	<b>-94.1</b>	<b>-65.78</b>	<b>8.3</b>

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 was 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 during the Ambulatory Period in the THS 2.2 Menthol arm remained decreased from baseline (721.15 ng/mg creat) and comparable to Day 5 (283.88 ng/mg creat), with values on Days 30, 60, and 90 of 369.55, 289.18, and 314.05 ng/mg creat, respectively. In the mCC arm, 3-HPMA values decreased from 777.25 ng/mg creat at baseline to 691.59, 580.28, and 606.10 ng/mg creat on Days 30, 60, and 90, respectively. These values corresponded to percent changes from baseline on Day 90 of -53.82% and -5.54% 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 (711.68 ng/mg creat) and comparable to Day 5 (151.43 ng/mg creat), as expected, with values on Days 30, 60, and 90 of 228.14, 219.07, and 177.90 ng/mg creat, respectively, corresponding to percent changes from baseline of -63.88%, -57.26%, and -57.21%, respectively.





Analysis of 3-HPMA urinary concentrations adjusted for creatinine and urinary quantity of MHBMA excreted over 24 hours for THS 2.2 Menthol users versus mCC use 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 [Table 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 65](#).

**Table 65 Analysis of 3-HPMA versus mCC on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean Ratio Geometric (THS m2.2:mCC)			
			LS Mean	(%)	CV(%)	95% CI
Quantity excreted over 24 hours (µg)	THS m2.2	45	503.29	51.90	51.59	41.11, 65.50
	mCC	29	969.81			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	43	310.81	52.02	53.49	40.80, 66.33
	mCC	29	597.49			

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; ANCOVA = analysis of covariance; CI = confidence interval; 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.

Data Source: [Appendix 15, Table 15.2.3.2](#) and [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 47.98% lower than that of subjects who continued to smoke mCC (95% CI: 33.67, 59.20; 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.

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 47.66% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 33.01, 59.11; 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 3-HPMA urinary concentration adjusted for creatinine in subjects



who switched to THS 2.2 Menthol being 48.49% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 33.25, 60.26; 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 66](#) presents the results of the S-PMA concentrations adjusted for creatinine at each time point in the Ambulatory Period by study arm.

**Table 66 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 (%)	CV		
					Min	Median	Max
THS m2.2	Baseline	65	1510.14	108.680	93.0	1776.79	9243.9
	Day 5	71	133.64	86.656	18.7	131.05	1269.2
	Day 30	39	320.57	175.349	43.7	280.36	3691.9
	Day 60	39	330.16	161.282	30.3	300.37	3810.7
	<b>Day 90</b>	<b>47</b>	<b>314.02</b>	<b>184.385</b>	<b>25.7</b>	<b>330.20</b>	<b>4007.9</b>
mCC	Baseline	30	1433.17	107.941	160.8	1486.69	4946.2
	Day 5	33	1062.05	189.124	118.7	1557.46	6677.6
	Day 30	32	1402.80	155.739	77.4	2161.42	5188.9
	Day 60	33	1152.49	139.241	127.1	1318.51	8145.4
	<b>Day 90</b>	<b>32</b>	<b>1218.56</b>	<b>151.051</b>	<b>127.1</b>	<b>1438.46</b>	<b>7266.2</b>
SA	Baseline	21	1488.78	102.283	213.5	1624.50	8015.0
	Day 5	22	133.11	99.339	20.9	123.18	1008.6
	Day 30	13	329.61	294.050	35.9	190.78	3307.4
	Day 60	11	230.52	278.640	18.7	256.34	3909.1
	<b>Day 90</b>	<b>9</b>	<b>181.62</b>	<b>179.279</b>	<b>27.7</b>	<b>202.61</b>	<b>1960.5</b>

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 67 presents overall percent change from baseline in S-PMA concentration adjusted for creatinine in the Ambulatory Period by study arm.

**Table 67 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		SD	Min	Median	Max
		Subjects	Mean				
THS m2.2	Day 5	65	-88.81	8.745	-98.5	-91.16	-57.6
	Day 30	36	-59.96	55.004	-99.1	-74.63	197.4
	Day 60	35	-59.95	64.071	-98.6	-77.64	-264.5
	Day 90	43	<b>-65.24</b>	<b>34.888</b>	<b>-98.8</b>	<b>-81.14</b>	<b>21.2</b>
mCC	Day 5	30	-12.55	42.740	-91.2	-0.64	71.6
	Day 30	29	15.56	60.720	-86.2	4.91	208.5
	Day 60	30	-0.40	58.640	-90.2	-19.25	186.7
	Day 90	29	<b>5.54</b>	<b>63.015</b>	<b>-80.6</b>	<b>-6.58</b>	<b>180.9</b>
SA	Day 5	21	-89.87	6.267	-97.2	-91.74	-70.7
	Day 30	12	-56.83	63.352	-96.9	-75.91	125.4
	Day 60	11	-50.57	75.367	-98.1	-77.98	166.4
	Day 90	9	<b>-64.63</b>	<b>41.226</b>	<b>-97.6</b>	<b>-74.98</b>	<b>33.6</b>

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 was 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 (1510.14 pg/mg creat) but higher than Day 5 (133.64 pg/mg creat), with values on Days 30, 60, and 90 of 320.57, 330.16, and 314.02 pg/mg creat, respectively. In the mCC arm, S-PMA values remained similar to baseline (1433.17 pg/mg creat) on Day 30 and decreased on Day 60 and Day 90, with levels of 1402.80, 1152.49, and 1218.56 pg/mg creat, respectively. These values corresponded to percent changes from baseline on Day 90 of -65.24% and 5.54% 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 (1488.78 pg/mg creat) but higher than Day 5 (133.11 pg/mg creat), with values on Days 30, 60, and 90 of 329.61, 230.52, and 181.62 pg/mg creat, respectively, corresponding to percent changes from baseline of -56.83%, -50.57%, and -64.63%, respectively.





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 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 [Table 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 68](#).

**Table 68 Analysis of S-PMA 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 (ng)	THS m2.2	45	465.32	23.53	137.61	14.36, 38.57
	mCC	29	1977.22			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	267.16	22.08	133.71	13.52, 36.06
	mCC	29	1209.91			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; PP = per protocol; 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 [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 77.92% lower than that of subjects who continued to smoke mCC (95% CI: 63.94, 86.48; 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.

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 77.61% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 63.14, 86.40; 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 77.67% lower than that of subjects who continued to smoke mCC on Day 90 (95% CI: 63.21, 86.45; 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 concentration adjusted for creatinine data during the course of the study 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](#).

[Table 69](#) presents the results of the Total NNAL concentrations adjusted for creatinine in the Confinement Period by study arm.



**Table 69 Absolute Values of Total NNAL 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	67	150.01	115.699	5.0	187.11	643.9
	Day 1	73	93.92	106.580	3.6	100.54	520.3
	Day 2	73	69.73	107.295	1.8	83.06	310.5
	Day 3	73	65.81	101.017	1.7	81.30	321.0
	Day 4	73	61.46	103.483	1.6	71.90	294.6
	Day 5	73	57.04	112.782	1.2	68.40	240.5
mCC	Baseline	30	147.90	115.044	15.3	136.01	1154.7
	Day 1	34	130.23	112.157	18.7	125.58	1154.7
	Day 2	34	125.05	117.871	14.1	121.03	1154.7
	Day 3	34	135.68	117.497	17.0	114.62	1154.7
	Day 4	34	127.23	123.388	14.8	124.17	1154.7
	Day 5	34	120.29	152.188	6.1	107.18	1154.7
SA	Baseline	21	142.18	112.752	35.3	118.29	979.6
	Day 1	22	97.33	110.314	15.5	84.82	820.4
	Day 2	22	72.13	123.800	14.3	63.51	640.4
	Day 3	22	68.23	115.612	16.8	67.73	604.2
	Day 4	22	55.67	140.921	7.1	61.69	505.0
	Day 5	22	54.74	118.058	11.9	53.99	392.4

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.](#)

[Table 70](#) presents overall percent change from baseline in Total NNAL concentration adjusted for creatinine in the Confinement Period by study arm.



**Table 70 Percent Change from Baseline Total NNAL Concentration Adjusted for Creatinine (pg/mg creat) 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	67	-34.61	22.375	-71.9	-38.80	67.8
	Day 2	67	-47.75	43.283	-79.8	-52.87	289.0
	Day 3	67	-52.70	26.313	-81.0	-56.32	125.5
	Day 4	67	-55.76	19.399	-88.1	-58.15	49.9
	Day 5	67	-60.23	14.023	-84.5	-60.03	16.3
mCC	Day 1	30	-1.61	27.833	-51.0	-2.25	69.1
	Day 2	30	-4.09	31.579	-46.7	-5.35	102.5
	Day 3	30	0.86	35.174	-50.6	-3.22	108.4
	Day 4	30	0.11	31.765	-52.8	-5.22	85.3
	Day 5	30	-5.58	38.839	-81.8	-5.20	114.0
SA	Day 1	21	-30.44	18.092	-61.1	-29.78	22.7
	Day 2	21	-45.69	16.969	-69.7	-48.22	6.4
	Day 3	21	-49.92	19.667	-71.3	-53.27	6.9
	Day 4	21	-57.87	18.452	-91.0	-61.80	-1.7
	Day 5	21	-58.86	17.834	-85.0	-61.45	-11.1

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 was 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 during the Confinement Period, 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 (150.01 pg/mg creat) to Day 5 (57.04 pg/mg creat) in contrast to Total NNAL values in the mCC arm, where only a small decrease from baseline (147.90 pg/mg creat) to Day 5 (120.29 pg/mg creat) was observed. Percent changes from baseline of -60.23% and -5.58% were observed 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 (-47.75%). In the SA arm, geometric mean Total NNAL values decreased from baseline (142.18 pg/mg creat) to Day 5 (54.74 pg/mg creat), as expected, which corresponded to a -58.86% change from baseline, with the majority of the decrease observed by Day 2.



Analysis of Total NNAL urinary concentrations adjusted for creatinine and urinary quantity of Total NNAL excreted over 24 hours for THS 2.2 Menthol users versus mCC use on Day 5 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 [Table 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 71](#).

**Table 71 Analysis of Total NNAL versus mCC on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS			
			Geometric LS Mean	Mean Ratio (THS m2.2:mCC) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	69	90.31			
	mCC	30	209.49	43.11	43.12	36.03, 51.58
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	55.44			
	mCC	30	126.55	43.81	40.70	36.92, 51.97

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 15.2.3.2](#) and [Table 15.2.3.4](#).

On Day 5, the LS mean of Total NNAL urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 56.19% lower than that of subjects who continued to smoke mCC (95% CI: 48.03, 63.08; 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.

An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.6](#)), with the LS mean of Total NNAL urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use being 55.45% lower than that of subjects who continued to smoke mCC on Day 5 (95% CI: 46.99, 62.56; p-value <0.001).

In addition, during the Confinement 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 Total NNAL urinary concentration adjusted for creatinine in subjects





who switched to THS 2.2 Menthol being 56.19% lower than that of subjects who continued to smoke mCC on Day 5 (95% CI: 48.03, 63.08; p-value <0.001).

#### 11.2.2 Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL During the Study 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 versus SA 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 on Day 5 is provided in [Table 72](#).

**Table 72 Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 versus SA (PP Set)**

Biomarker/ Time point	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA)	CV (%)	95% CI
				(%)		
Evening COHb (%)						
Day 5	THS m2.2	74	2.33	97.30	26.50	86.02, 110.05
	SA	23	2.39			
Urinary MHBMA (pg/mg creat)						
Day 5	THS m2.2	65	110.96	116.84	76.92	83.12, 164.24
	SA	21	94.97			
Urinary MHBMA (ng)						
Day 5	THS m2.2	67	181.31	116.29	76.87	82.84, 163.26
	SA	21	155.91			
Urinary 3-HPMA (ng/mg creat)						
Day 5	THS m2.2	67	278.13	182.92	36.45	153.51, 217.97
	SA	21	152.05			
Urinary 3-HPMA (µg)						
Day 5	THS m2.2	70	461.90	179.38	39.63	149.05, 215.86
	SA	22	257.50			

**Table 72 Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5 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) (%)		
Urinary S-PMA (pg/mg creat)						
Day 5	THS m2.2	65	134.11	102.34	69.68	74.82, 139.37
	SA	21	131.05			
Urinary S-PMA (ng)						
Day 5	THS m2.2	67	223.78	102.78	71.62	74.69, 141.42
	SA	21	217.73			
Total NNAL (pg/mg creat)						
Day 5	THS m2.2	67	55.44	99.99	40.70	82.32, 121.44
	SA	21	55.44			
Total NNAL (ng)						
Day 5	THS m2.2	69	90.31	98.56	43.12	80.35, 120.88
	SA	21	91.63			

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 use and subjects who abstained from smoking for evening COHb and urinary concentrations of MHBMA, S-PMA, and Total NNAL 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 83% higher than that of subjects who abstained from smoking, with the lower limit of the 95% CI being greater than 100% ([Table 72](#)).

Results of the analyses of urinary concentrations excreted over 24 hours versus SA were consistent with the results for the concentrations adjusted for creatinine.



An additional sensitivity analysis using a mixed model approach showed consistent results ([Appendix 15, Table 15.2.3.6](#)) to those shown in [Table 72](#).

Data for the PP Set on Day 90 is provided in [Table 73](#).

**Table 73 Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 90 versus SA (PP Set)**

				Geometric LS		
		Number	Mean Ratio			
Biomarker/ Time point	Exposure	of Subjects	Geometric LS Mean	(THS m2.2:SA) (%)	CV (%)	95% CI
Evening COHb (%)						
Day 90	THS m2.2	47	2.65	90.50	36.30	69.88, 117.19
	SA	9	2.92			
Urinary MHBMA (pg/mg creat)						
Day 90	THS m2.2	43	213.78	64.77	85.36	36.88, 113.74
	SA	9	330.06			
Urinary MHBMA (ng)						
Day 90	THS m2.2	45	364.12	67.40	87.08	38.05, 119.37
	SA	9	540.23			
Urinary 3-HPMA (ng/mg creat)						
Day 90	THS m2.2	43	310.81	147.34	53.49	101.23, 214.45
	SA	9	210.94			
Urinary 3-HPMA (µg)						
Day 90	THS m2.2	45	503.29	147.91	51.59	102.85, 212.72
	SA	9	340.26			
Urinary S-PMA (pg/mg creat)						
Day 90	THS m2.2	43	267.16	117.51	133.71	55.32, 249.57
	SA	9	227.36			
Urinary S-PMA (ng)						
Day 90	THS m2.2	45	465.32	122.97	137.61	57.16, 264.55
	SA	9	378.40			

**Table 73 Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 90 versus SA (PP Set)**

			Geometric LS			
Biomarker/ Time point		Number of Subjects	Geometric LS Mean	Mean Ratio (THS m2.2:SA) (%)	CV (%)	95% CI
Total NNAL (pg/mg creat)						
Day 90	THS m2.2	43	41.05	75.98	106.00	39.92, 144.61
	SA	9	54.03			
Total NNAL (ng)						
Day 90	THS m2.2	45	67.01	76.66	112.58	39.29, 149.56
	SA	9	87.42			

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](#).

Due to the limited number of subjects in the SA arm for the PP Set on Day 90 (N = 9), the results should be interpreted with caution and broad 95% CIs were observed for most assessments. There were no notable differences observed between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking for evening COHb and urinary concentrations of MHBMA, S-PMA, and Total NNAL adjusted for creatinine on Day 90, with the 95% CIs for these parameters spanning 100%.

For urinary 3-HPMA adjusted for creatinine on Day 90, the LS means in subjects who switched to THS 2.2 Menthol use was approximately 47% higher than that of subjects who abstained from smoking, with the lower limit of the 95% CI being greater than 100% ([Table 73](#)).

Results of the analyses of urinary concentrations excreted over 24 hours versus SA were consistent with the results for the concentrations adjusted for creatinine.

An additional sensitivity analysis using a mixed model approach and analysis using the Compliant Population ([Appendix 15, Table 15.2.3.6](#) and [Table 15.2.3.7](#)) showed consistent results to those shown in [Table 73](#).

Due to non-compliance the number of subjects in the FAS was higher than the number of subjects in the PP Set. Therefore, the results from the FAS differed from the results presented in [Table 73](#) ([Appendix 15, Table 15.2.3.3](#)). For COHb and MHBMA, and Total





NNAL concentration adjusted for creatinine, the values were lower for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking, with the upper limit of the 95% CIs below 100%. For S-PMA adjusted for creatinine, levels were lower in the THS 2.2 Menthol arm compared to the SA arm in the FAS, whereas levels were higher in the THS 2.2 Menthol arm compared to the SA arm for the PP Set, although the 95% CIs spanned 100% for both analysis populations. For 3-HPMA adjusted for creatinine in the FAS, the LS means in subjects who switched to THS 2.2 Menthol use was only 8% higher than that of subjects who abstained from smoking (compared to 47% in the PP Set), with the 95% CI spanning 100%.

### 11.2.3 Analysis of Other Biomarkers of Exposure During Study

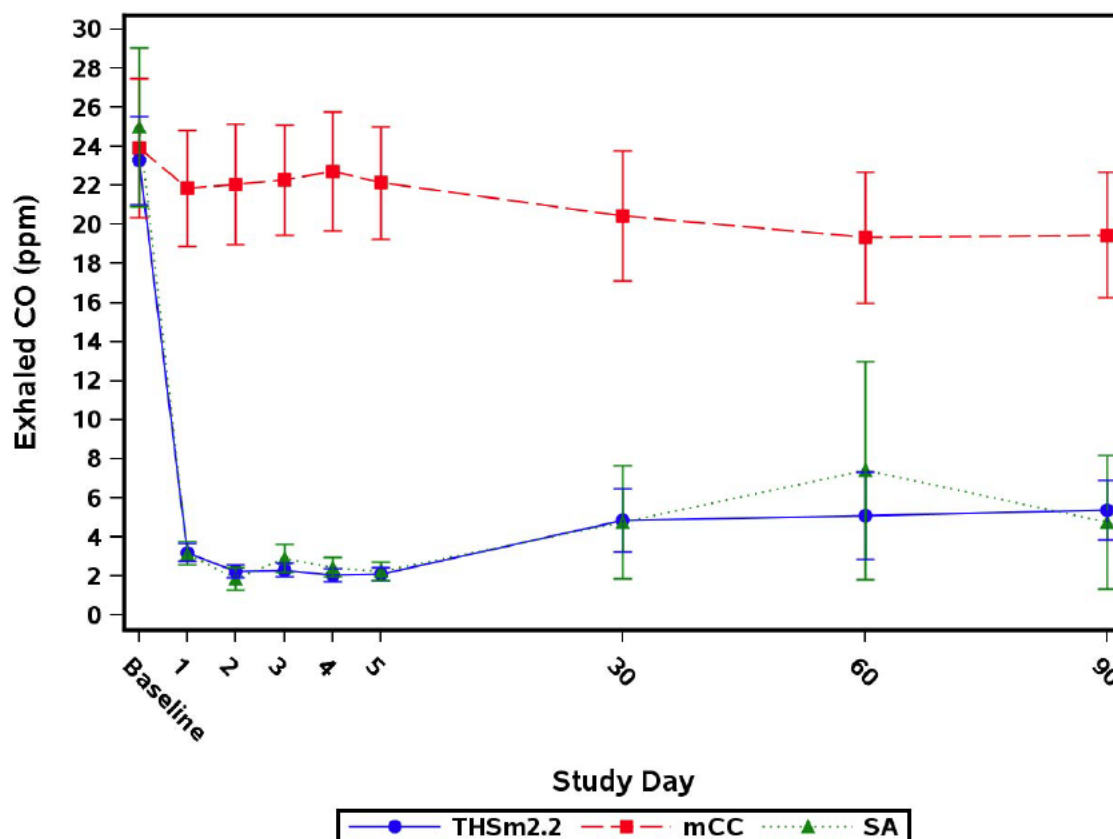
#### 11.2.3.1 Exhaled Carbon Monoxide During Study

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 percent 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. Data for the PP Set is 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 was the last assessment prior to first 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.

CO on Baseline and Days 1 - 5 represent the evening sample collected.

Baseline was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of the mean exhaled CO in 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 observed on Day 2, before plateauing during the Confinement Period.

Arithmetic mean exhaled CO values decreased in the THS 2.2 Menthol arm from the evening of Day 0 (23.28 ppm) to the evening of Day 5 (2.11 ppm), in contrast to exhaled CO in the mCC arm, which remained similar from the evening of Day 0 (23.91 ppm) to the evening of Day 5 (22.14 ppm). These values corresponded to percent time-matched changes from baseline of -88.55% and 23.13% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, arithmetic mean exhaled CO values decreased from Day 0



(25.00 ppm) to Day 5 (2.25 ppm), as expected, which corresponded to a -88.70% 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 (4.85, 5.10, and 5.38 ppm, respectively) but higher than the Day 5 value. Exhaled CO in the mCC arm remained at approximate baseline levels on Days 30, 60, and 90 (20.44, 19.34, and 19.47 ppm, respectively). These values corresponded to percent time-matched changes from baseline on Day 90 of -72.67% and -4.77% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean exhaled CO values during the Ambulatory Period remained decreased from baseline on Days 30, 60, and 90 (4.77, 7.42, and 4.78 ppm, respectively), as expected, which corresponded to a -35.50% change from baseline on Day 90.

Analyses of exhaled CO for THS 2.2 use versus mCC use and versus SA on Day 5 and Day 90 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 on Day 5 are presented in [Table 74](#).

**Table 74 Analysis of Exhaled CO (ppm) versus mCC and SA on Day 5 (PP Set)**

Exposure	Number of Subjects	LS Mean	THS m2.2 - mCC difference (ppm)	95% CI
THS m2.2	75	2.20	-19.96	-21.62, -18.31
mCC	35	22.16		

Exposure	Number of Subjects	LS Mean	THS m2.2 – SA difference (ppm)	95% CI
THS m2.2	75	2.20	0.17	-1.72, 2.07
SA	24	2.03		

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 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 -19.96 ppm (95% CI: -21.62, -18.31; 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% CIs of the difference in LS means spanning 0.

The sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the difference in LS means of exhaled CO in subjects who switched to THS 2.2 Menthol use compared to those who abstained from smoking was -2.54 ppm (95% CI: -4.91, -0.18).

Data for the PP Set on Day 90 are presented in [Table 75](#).

**Table 75 Analysis of Exhaled CO versus mCC and SA on Day 90 (PP Set)**

Exposure	Number of Subjects	LS Mean	THS m2.2 - mCC difference	95% CI
THS m2.2	47	4.99		
mCC	32	19.61	-14.62	-17.67, -11.57

Exposure	Number of Subjects	LS Mean	THS m2.2 – SA difference	95% CI
THS m2.2	47	4.99		
SA	9	5.09	-0.10	-4.99, 4.78

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 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 -14.62 (95% CI: -17.67, -11.57; 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 the 95% CIs of the difference in LS means spanning 0.

The sensitivity analysis on the Compliant Population and the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the difference in LS means of exhaled CO in





subjects who switched to THS 2.2 Menthol use compared to those who abstained from smoking was -4.54 ppm (95% CI: -7.40, -1.68).

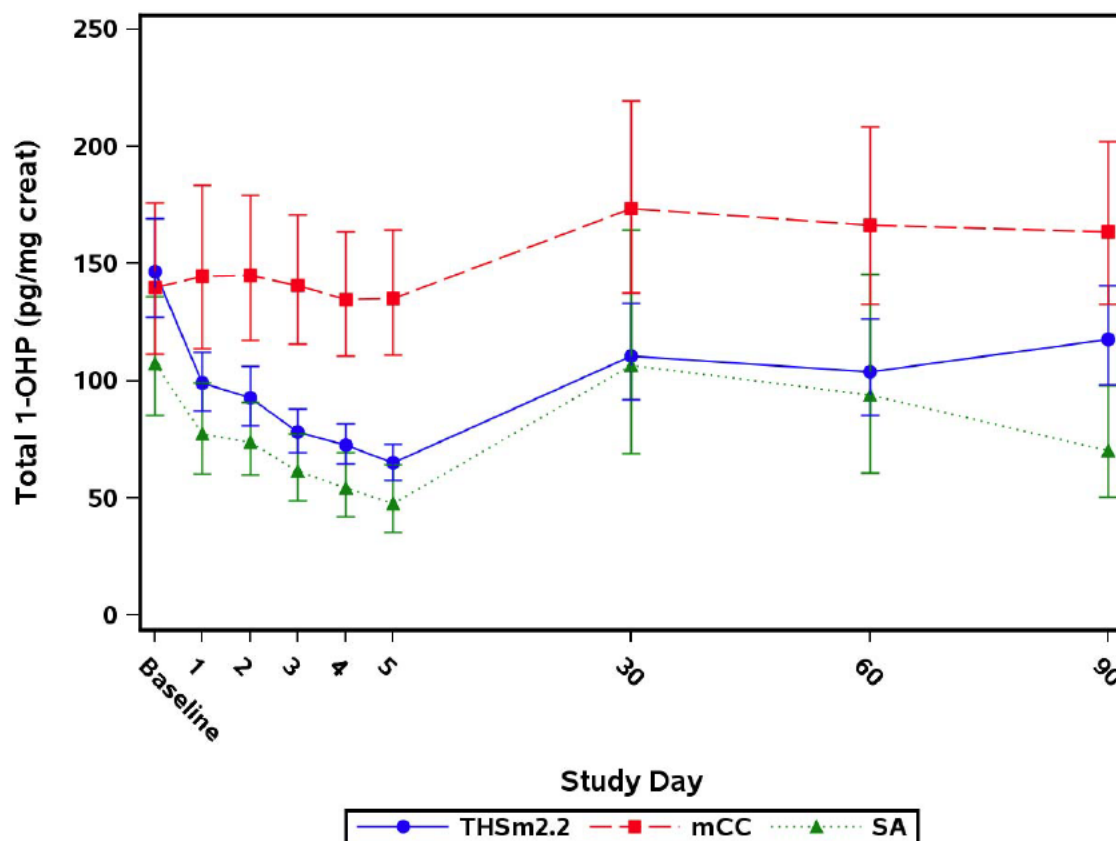
#### 11.2.3.2 Total 1-hydroxypyrene in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 10](#).



**Figure 10 Geometric Mean and 95% CI Total 1-OHP Urinary 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 was the last assessment prior to first 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 was 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 1-OHP in the THS 2.2 Menthol arm was comparable to that of the SA arm in the Confinement Period, with a gradual decline from baseline observed from Days 1 to 5. Geometric mean Total 1-OHP values in the THS 2.2 Menthol arm decreased from baseline (146.56 pg/mg creat) to Day 5 (64.87 pg/mg creat) whereas Total 1-OHP in the mCC arm decreased only slightly from baseline (139.92 pg/mg creat) to Day 5 (135.14 pg/mg creat). These values corresponded to percent changes from baseline of -53.41% and -4.82% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total 1-OHP values also decreased from baseline



(107.62 pg/mg creat) to Day 5 (47.80 pg/mg creat), as expected, which corresponded to a -53.14% 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 (110.67, 103.84, and 117.77 pg/mg creat, respectively) but were higher than the Day 5 value. Total 1-OHP in the mCC arm was higher than during the Confinement Period on Days 30, 60, and 90 (173.68, 166.40, and 163.80 pg/mg creat, respectively). These values corresponded to percent time-matched changes from baseline on Day 90 of -14.61% and 26.54% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, mean Total 1-OHP values had returned to approximate baseline value on Day 30 (106.74 pg/mg creat) before decreasing to Day 60 and 90 (94.00 and 70.19 pg/mg creat, respectively), which corresponded to a -19.83% change from baseline on Day 90.

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 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 on Day 5 are presented in [Table 76](#).

**Table 76 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	66	101.23	48.36	37.61	41.22, 56.72
	mCC	30	209.34			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	65	60.41	48.11	31.01	42.11, 54.96
	mCC	30	125.57			

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	66	101.23	107.54	37.61	89.58, 129.11
	SA	22	94.13			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	65	60.41	104.96	31.01	90.17, 122.16
	SA	22	57.56			

Abbreviations: 1-OHP = 1-hydroxypyrene; 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 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 15.2.3.4](#).

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 51.89% lower than that of subjects who continued to smoke mCC (95% CI: 45.04, 57.89; 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.

Data for the PP Set on Day 90 are presented in [Table 77](#).

**Table 77 Analysis of Total 1-OHP versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean Ratio			
			Geometric LS Mean	(THS m2.2:mCC) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	44	179.24	67.70	50.27	53.62, 85.48
	mCC	29	264.76			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	108.70	66.46	49.92	52.67, 83.84
	mCC	29	163.56			

Parameter	Exposure	Number of Subjects	Geometric LS Mean Ratio			
			Geometric LS Mean	(THS m2.2:SA) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	44	179.24	117.60	50.27	81.25, 170.21
	SA	9	152.42			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	108.70	114.73	49.92	79.83, 164.88
	SA	9	94.74			

Abbreviations: 1-OHP = 1-hydroxypyrene; 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 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 15.2.3.4](#).

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 33.54% lower than that of subjects who continued to smoke mCC (95% CI: 16.16, 47.33; 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.

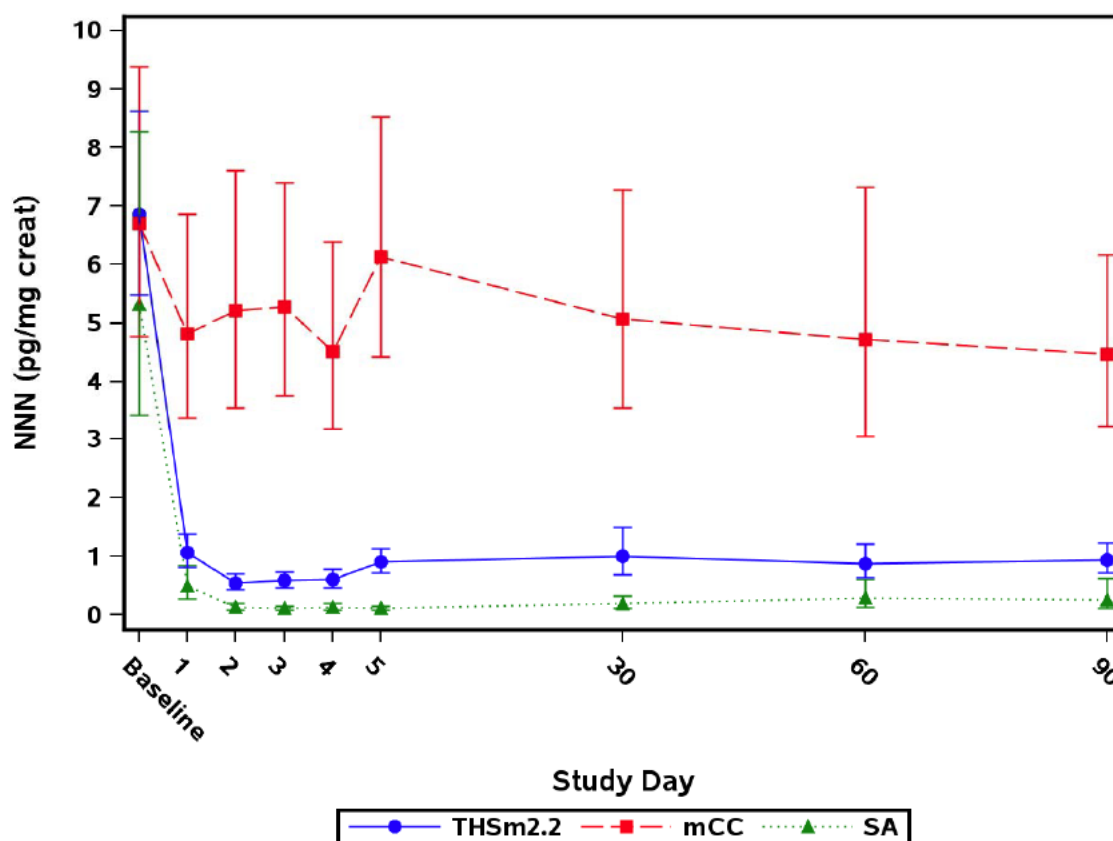
#### 11.2.3.3 Total N-nitrosornicotine in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 11](#).



**Figure 11 Geometric Mean and 95% CI Total NNN Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; NNN = N-nitrosornicotine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol; Total NNN = N-nitrosornicotine. Baseline was the last assessment prior to first 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 was 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 THS 2.2 Menthol arm in the Confinement Period was similar to that of the SA arm, with the majority of the decrease from baseline being achieved by Day 1, before plateauing thereafter from Days 2 to 5. Geometric mean Total NNN values decreased in the THS 2.2 Menthol arm from baseline (6.87 pg/mg creat) to Day 5 (0.90 pg/mg creat) in contrast to Total NNN in the mCC arm, where values were comparable to baseline (6.70 pg/mg creat) on Day 5 (6.14 pg/mg creat). These values corresponded to percent changes from baseline of -79.62% and 8.94% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean Total NNN values



decreased from baseline (5.32 pg/mg creat) to Day 5 (0.12 pg/mg creat), as expected, which corresponded to a -96.64% change from baseline.

During the Ambulatory Period, Total NNN remained reduced from baseline and comparable to the Day 5 values for the THS 2.2 Menthol and SA study arms with changes from baseline of -82.37% and -80.54%, respectively, on Day 90. In the mCC arm, Total NNN gradually decreased from the Day 5 value on Days 30, 60, and 90, with a change from baseline of -1.49% on Day 90.

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 on Day 5 are also tabulated in [Table 78](#).



**Table 78 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)			95% CI
				(%)	CV (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	69	1.46	13.92	82.33		10.18, 19.03
	mCC	30	10.50				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	0.91	14.06	78.93		10.38, 19.06
	mCC	30	6.44				

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	69	1.46	674.45	82.33		471.67, 964.39
	SA	21	0.22				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	0.91	678.32	78.93		479.07, 960.44
	SA	21	0.13				

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; 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 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 15.2.3.4](#).

On Day 5, the LS mean of Total NNN concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 85.94% lower than that of subjects who continued to smoke mCC (95% CI: 80.94, 89.62; 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 6.78-fold higher than that of subjects who abstained from smoking (95% CI: 479.07, 960.44). 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.

Data for the PP Set on Day 90 are presented in [Table 79](#).

**Table 79 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)			95% CI
				LS Mean	(%)	CV (%)	
Quantity excreted over 24 hours (ng)	THS m2.2	45	1.47		18.45	90.58	12.70, 26.79
	mCC	29	7.95				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	0.90		17.80	87.18	12.31, 25.75
	mCC	29	5.04				

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	45	1.47		279.26	90.58	157.17, 496.18
	SA	9	0.53				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	0.90		268.55	87.18	153.11, 471.04
	SA	9	0.33				

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; LS = least squares; mCC = Menthol conventional cigarette; NNN = N-nitrosornornicotine; 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.

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 82.20% lower than that of subjects who



continued to smoke mCC (95% CI: 74.25, 87.69; 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 higher in subjects who switched to THS 2.2 Menthol use compared to that of subjects who abstained from smoking (2.69-fold, with 95% CI of 153.11, 471.04 for concentrations adjusted for creatinine).

The sensitivity analysis on the Compliant Population and the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS means of both Total NNN 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%.

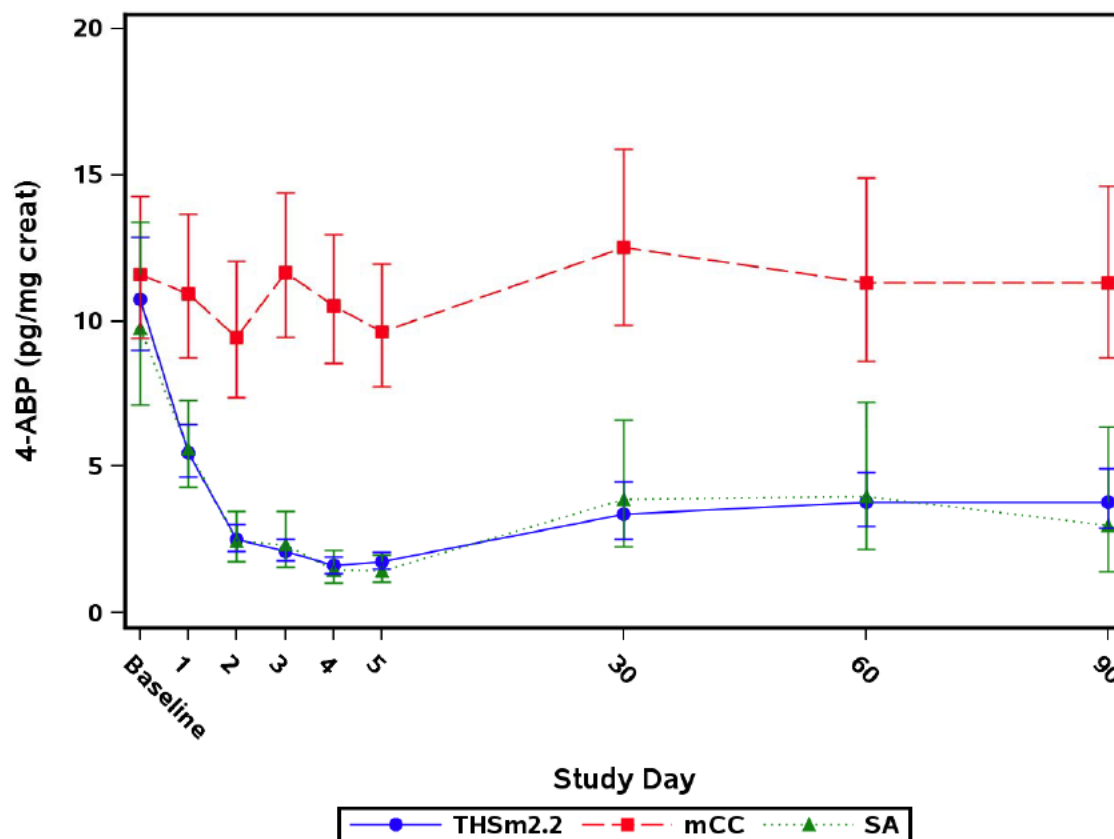
#### 11.2.3.4 4-aminobiphenyl in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 12](#).



**Figure 12 Geometric Mean and 95% CI 4-ABP Urinary 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 was the last assessment prior to first 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 was 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 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 (10.76 pg/mg creat) to Day 5 (1.76 pg/mg creat), in contrast to 4-ABP in the mCC arm, which slightly decreased from baseline (11.59 pg/mg creat) to Day 5 (9.63 pg/mg creat). These values corresponded to percent changes from baseline of -73.48% and -7.13% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 4-ABP values decreased from baseline (9.78 pg/mg creat) to Day 5 (1.44 pg/mg creat), as expected, which corresponded to a -80.83% change from baseline.





During the Ambulatory Period, 4-ABP remained reduced from baseline but higher than Day 5 values for the THS 2.2 Menthol and SA study arms, with changes from baseline of -54.19% and -35.58%, respectively, on Day 90. In contrast, 4-ABP in the mCC arm was comparable to baseline on Day 30 and remained relatively stable for the remainder of the Ambulatory Period, with a change from baseline of 22.21% observed on Day 90.

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 on Day 5 are presented in [Table 80](#).

**Table 80 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			95% CI
				(THS m2.2:mCC)	CV (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	70	3.13	19.48	63.42		15.18, 24.99
	mCC	31	16.05				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	1.86	19.31	64.86		14.90, 25.01
	mCC	30	9.63				

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio			95% CI
				(THS m2.2:SA)	CV (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	70	3.13	125.86	63.42		94.90, 166.92
	SA	22	2.48				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	1.86	120.62	64.86		89.83, 161.97
	SA	21	1.54				

Abbreviations: 4-ABP = 4-aminobiphenyl; 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 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 15.2.3.4](#).

On Day 5, the LS mean of 4-ABP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 80.69% lower than that of subjects who continued to smoke mCC (95% CI: 74.99, 85.10; 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, there was no notable difference in the LS means of 4-ABP concentration adjusted for creatinine and quantity excreted over 24 hours 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, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

Data for the PP Set on Day 90 are presented in [Table 81](#).

**Table 81 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	CV (%)	95% CI
				(THS m2.2:mCC) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	45	5.60	30.01	93.89	20.50, 43.94
	mCC	29	18.67			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	3.30	28.48	91.54	19.51, 41.58
	mCC	29	11.57			

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	45	5.60	111.97	93.89	62.01, 202.16
	SA	9	5.01			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	3.30	101.66	91.54	56.81, 181.90
	SA	9	3.24			

Abbreviations: 4-ABP = 4-aminobiphenyl; 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 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 15.2.3.4](#).

On Day 90, the LS mean of 4-ABP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 71.52% lower than that of subjects who continued to smoke mCC (95% CI: 58.42, 80.49; 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 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%.

The sensitivity analysis on the Compliant Population and the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS mean of 4-ABP concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 30.71% lower than that of subjects who abstained from smoking (95% CI: 4.46, 49.76).

#### 11.2.3.5 1-aminonaphthalene in 24-hour Urine During the Study

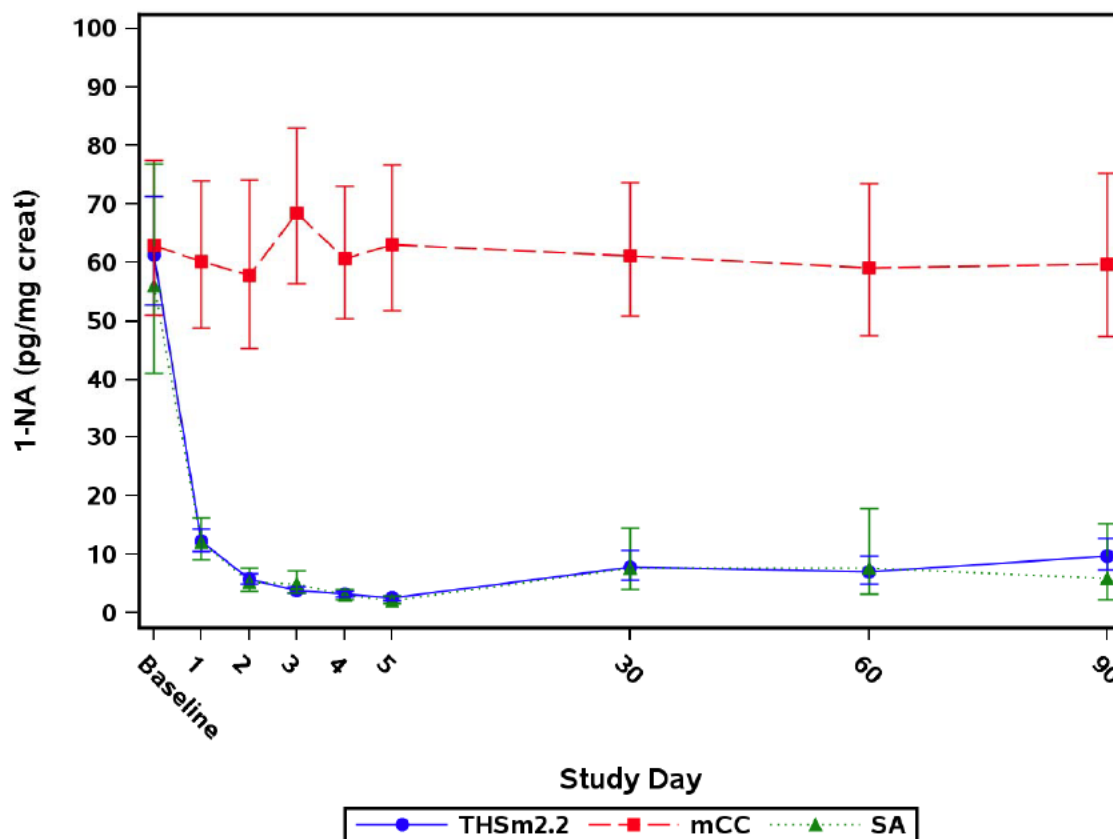
Subject listings of 1-NA data are provided in [Appendix 15, Listing 15.3.3.1](#).

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 13](#).





**Figure 13 Geometric Mean and 95% CI 1-NA Urinary 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 was the last assessment prior to first 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 was 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 (61.36 pg/mg creat) to Day 5 (2.51 pg/mg creat) whereas 1-NA values in the mCC arm remained similar from baseline (62.93 pg/mg creat) to Day 5 (63.05 pg/mg creat). These values corresponded to percent changes from baseline of -94.30% and 13.02% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 1-NA values decreased from baseline



(56.16 pg/mg creat) to Day 5 (2.17 pg/mg creat), as expected, which corresponded to a -94.00% change from baseline.

During the Ambulatory Period, 1-NA remained reduced from baseline but higher than Day 5 values for the THS 2.2 Menthol and SA study arms, with changes from baseline of -77.41% and -77.53%, respectively, on Day 90. In contrast, 1-NA in the mCC arm was comparable to baseline on Day 30 and remained relatively stable for the remainder of the Ambulatory Period, with a change from baseline of 14.16% observed on Day 90.

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 on Day 5 are presented in [Table 82](#).

**Table 82 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	70	4.35	4.07	55.99	3.25, 5.10
	mCC	31	106.92			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	2.67	4.15	57.67	3.28, 5.25
	mCC	30	64.48			

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	4.35	117.94	55.99	91.53, 151.98
	SA	22	3.69			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	2.67	116.96	57.67	89.59, 152.70
	SA	21	2.29			

Abbreviations: 1-NA = 1-aminonaphthalene; 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 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 15.2.3.4](#).

On Day 5, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 95.85% lower than that of subjects who continued to smoke mCC (95% CI: 94.75, 96.72; 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%.



The sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 29.42% lower than that of subjects who abstained from smoking (95% CI: 2.02, 49.16).

Data for the PP Set on Day 90 are presented in [Table 83](#).

**Table 83 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		CV (%)	95% CI
				(THS m2.2:mCC)	(%)		
Quantity excreted over 24 hours (ng)	THS m2.2	45	14.67	14.98	105.15	9.90, 22.65	
	mCC	29	97.96				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	8.67	14.29	102.76	9.47, 21.56	
	mCC	29	60.70				

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	45	14.67	145.18	105.15	76.43, 275.78	
	SA	9	10.11				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	8.67	133.95	102.76	71.10, 252.34	
	SA	9	6.48				

Abbreviations: 1-NA = 1-aminonaphthalene; 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 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 15.2.3.4](#).





On Day 90, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 85.71% lower than that of subjects who continued to smoke mCC (95% CI: 78.44, 90.53; 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 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%.

The sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented. The sensitivity analysis on the Compliant Population was consistent with the result from the PP Set for the THS 2.2 Menthol versus mCC comparison. For the THS 2.2 Menthol versus SA comparison in the Compliant Population, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 2.05-fold higher than that of subjects who abstained from smoking (95% CI: 107.08, 392.06).

For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS mean of 1-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 40.12% lower than that of subjects who abstained from smoking (95% CI: 14.19, 58.22).

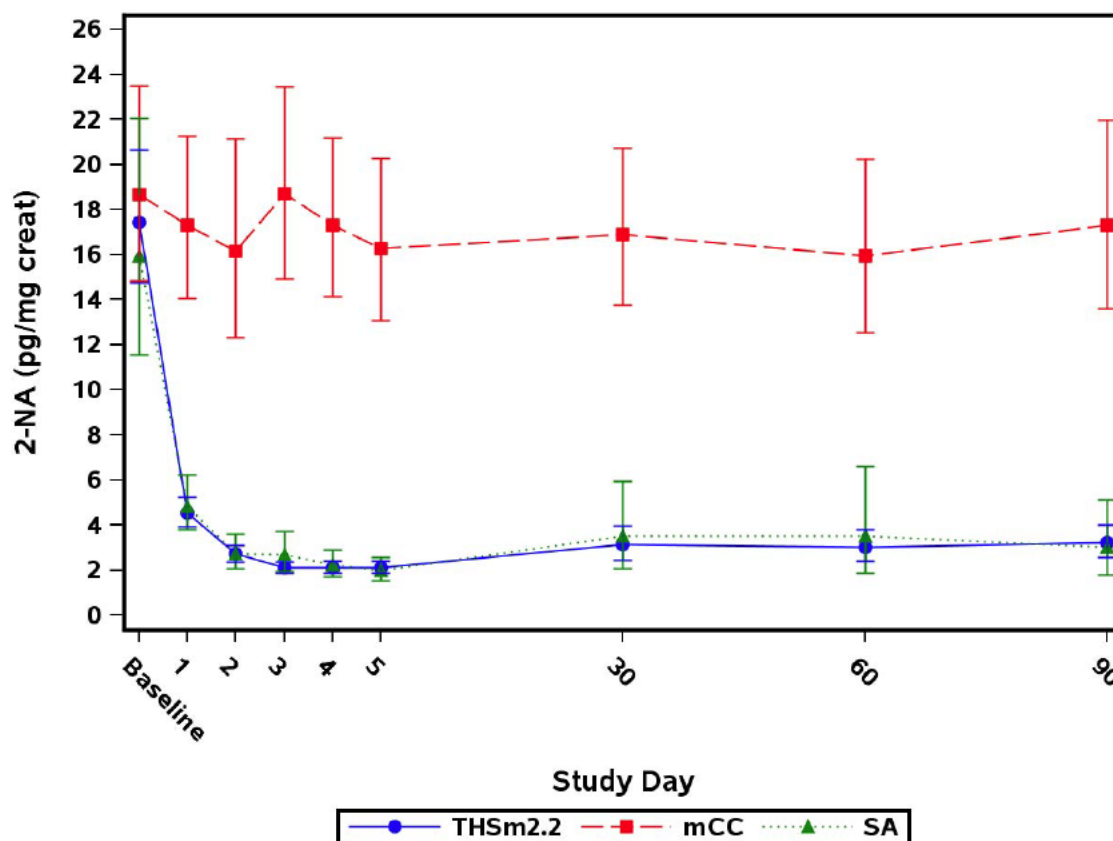
#### 11.2.3.6 2-aminonaphthalene in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 14](#).



**Figure 14 Geometric Mean and 95% CI 2-NA Urinary 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 was the last assessment prior to first 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 was 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 arm, with a sharp decline on Day 1 and a further small decrease observed on Day 2, before plateauing thereafter. Geometric means of 2-NA decreased in the THS 2.2 study arm from baseline (17.45 pg/mg creat) to Day 5 (2.10 pg/mg creat), whereas 2-NA in the mCC arm remained comparable to baseline (18.65 pg/mg creat) on Day 5 (16.28 pg/mg creat). These values corresponded to percent changes from baseline of -80.97% and 0.23% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean 2-NA values also decreased from baseline (15.97 pg/mg creat)



to Day 5 (1.98 pg/mg creat), as expected, which corresponded to a -82.14% change from baseline.

During the Ambulatory Period, 2-NA remained reduced from baseline but higher than Day 5 values for the THS 2.2 Menthol and SA study arms, with changes from baseline of -77.01% and -64.26%, respectively, on Day 90. In contrast, 2-NA in the mCC arm was comparable to baseline on Day 30 and remained relatively stable for the remainder of the Ambulatory Period, with a change from baseline of 11.04% observed on Day 90.

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 on Day 5 are presented in [Table 84](#).

**Table 84 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	70	3.62	12.78	51.14		10.40, 15.72
	mCC	31	28.33				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	2.24	13.12	54.65		10.49, 16.40
	mCC	30	17.11				

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	3.62	108.89	51.14		86.17, 137.59
	SA	22	3.33				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	2.24	109.03	54.65		84.55, 140.59
	SA	21	2.06				

Abbreviations: 2-NA = 2-aminonaphthalene; 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 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 15.2.3.4](#).

On Day 5, the LS mean of 2-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 86.88% lower than that of subjects who continued to smoke mCC (95% CI: 83.60, 89.51; 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.

Data for the PP Set on Day 90 are presented in [Table 85](#).

**Table 85 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	CV (%)	95% CI
				(THS m2.2:mCC) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	45	4.83	17.06	74.20	12.41, 23.43
	mCC	29	28.30			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	2.82	16.04	68.65	11.87, 21.67
	mCC	29	17.57			

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	45	4.83	90.70	74.20	55.41, 148.45
	SA	9	5.32			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	2.82	83.61	68.65	52.57, 132.97
	SA	9	3.37			

Abbreviations: 2-NA = 2-aminonaphthalene; 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 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 15.2.3.4](#).

On Day 90, the LS mean of 2-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 83.96% lower than that of subjects who continued to smoke mCC (95% CI: 78.33, 88.13; 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%.

The sensitivity analysis on the Compliant Population and the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS mean of 2-NA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 42.85% lower than that of subjects who abstained from smoking (95% CI: 24.43, 56.79).

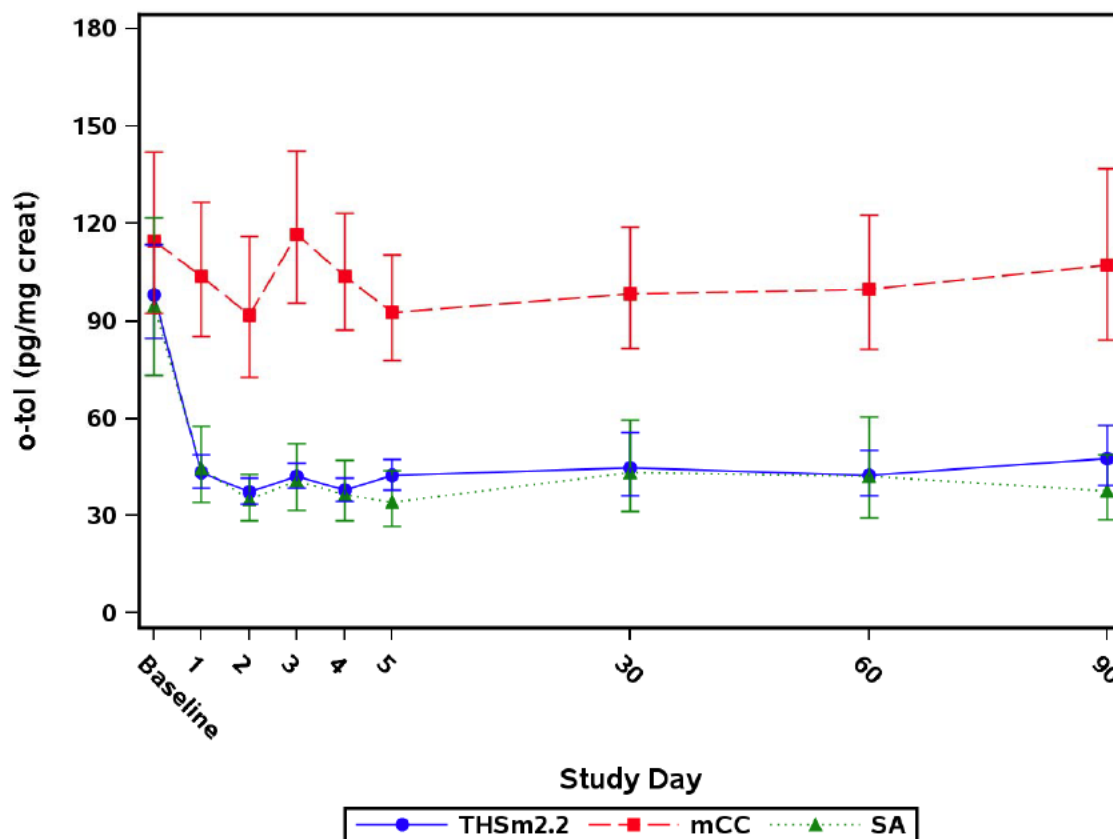
#### 11.2.3.7 o-toluidine in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 15](#).



**Figure 15 Geometric Mean and 95% CI o-tol Urinary 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; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was the last assessment prior to first 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 was 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 THS 2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Day 1 and a further small decrease observed on Day 2, before plateauing during the Confinement Period. Geometric mean o-toluidine values decreased in the THS 2.2 Menthol arm from baseline (98.12 pg/mg creat) to Day 5 (42.20 pg/mg creat), in contrast o-toluidine in the mCC arm was similar to baseline (114.59 pg/mg creat) on Day 5 (92.68 pg/mg creat). These values corresponded to percent changes from baseline of -40.73% and -10.68% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean o-toluidine values decreased from baseline



(94.65 pg/mg creat) to Day 5 (34.05 pg/mg creat), as expected, which corresponded to a -54.59% change from baseline.

During the Ambulatory Period, o-toluidine remained reduced from baseline but higher than Day 5 values for the THS 2.2 Menthol and SA arms, with changes from baseline of -20.76% and -46.88%, respectively, on Day 90. In contrast, o-toluidine in the mCC arm was comparable to baseline on Day 30 and remained relatively stable for the remainder of the Ambulatory Period, with a change from baseline of 10.33% observed on Day 90.

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 on Day 5 are presented in [Table 86](#).



**Table 86 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) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	72.02	47.32	48.14	38.89, 57.58
	mCC	31	152.19			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	44.82	48.72	49.32	39.70, 59.79
	mCC	30	91.98			

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	72.02	127.23	48.14	101.96, 158.76
	SA	22	56.60			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	44.82	128.72	49.32	102.10, 162.28
	SA	21	34.82			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; 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 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 15.2.3.4](#).

On Day 5, the LS mean of o-toluidine concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 51.28% lower than that of subjects who continued to smoke mCC (95% CI: 40.21, 60.30; 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 mean of o-toluidine concentration adjusted for creatinine was 28.72% higher than that of subjects who abstained from smoking (95% CI: 102.10, 162.28). The results for the quantity of o-toluidine 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.

Data for the PP Set on Day 90 are presented in [Table 87](#).

**Table 87 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	CV (%)	95% CI
				(THS m2.2:mCC) (%)		
Quantity excreted over 24 hours (ng)	THS m2.2	45	75.39	43.18	66.17	32.28, 57.75
	mCC	29	174.61			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	47.06	43.29	68.48	32.00, 58.55
	mCC	29	108.71			

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	45	75.39	113.36	66.17	72.62, 176.96
	SA	9	66.50			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	47.06	112.05	68.48	70.79, 177.37
	SA	9	42.00			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; 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 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 15.2.3.4](#).

On Day 90, the LS mean of o-toluidine concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 56.71% lower than that of subjects who continued to smoke mCC (95% CI: 41.45, 68.00; 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.

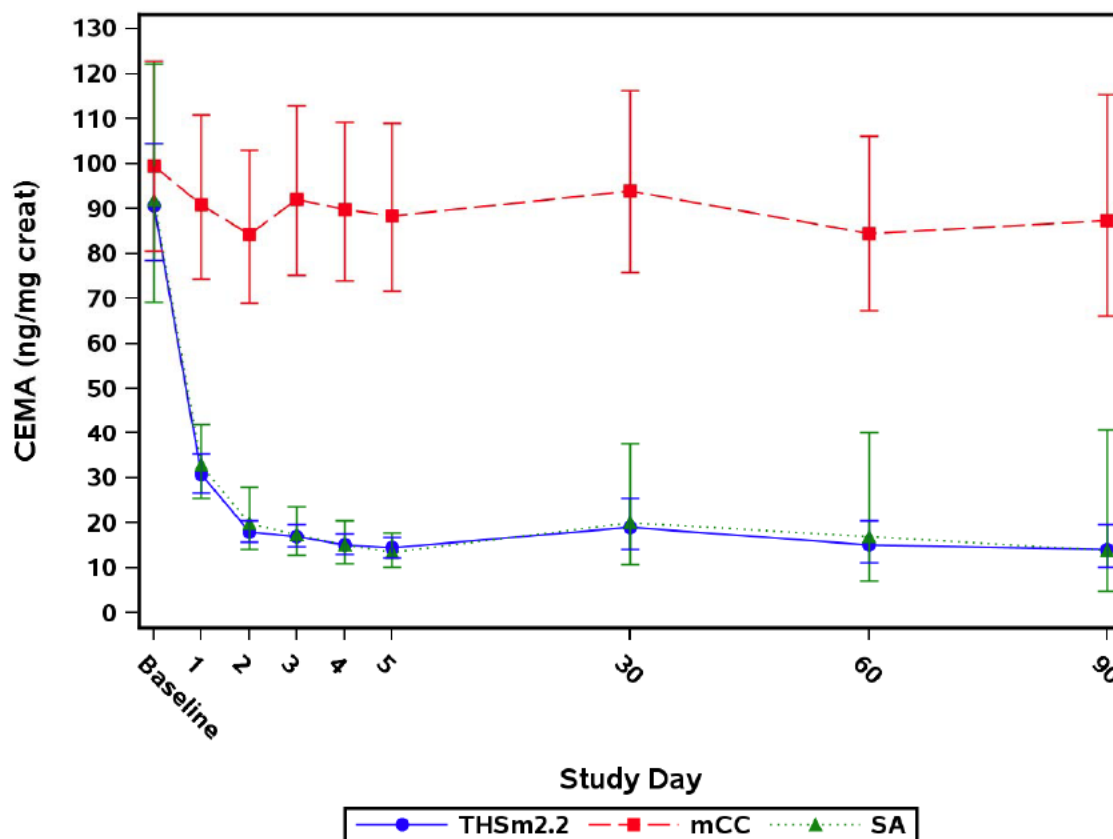
#### 11.2.3.8 2-cyanoethylmercapturic acid in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 16](#).



**Figure 16 Geometric Mean and 95% CI CEMA Urinary 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 was the last assessment prior to first 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 was 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 (90.62 ng/mg creat) to Day 5 (14.39 ng/mg creat) whereas CEMA values in the mCC arm remained similar to baseline (99.50 ng/mg creat) on Day 5 (88.40 ng/mg creat). These values correspond to percent changes from baseline of -83.00% and -9.05% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean CEMA values decreased from baseline (91.97 ng/mg creat) to Day 5 (13.40 ng/mg creat), as expected, which corresponded to a -83.83% change from baseline.





During the Ambulatory Period, CEMA remained reduced from baseline, with changes from baseline of -76.58% and -65.96%, respectively, on Day 90. In contrast, CEMA in the mCC arm was comparable to baseline on Day 30 and remained relatively stable for the remainder of the Ambulatory Period, with a change from baseline of 2.56% observed on Day 90.

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 on Day 5 are presented in [Table 88](#).

**Table 88 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	70	23.56	17.21	45.68	14.28, 20.74
	mCC	31	136.87			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	67	13.98	17.23	42.01	14.44, 20.55
	mCC	30	81.15			

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	23.56	105.70	45.68	85.60, 130.53
	SA	22	22.29			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	67	13.98	105.84	42.01	86.65, 129.27
	SA	21	13.21			

Abbreviations: ANCOVA = analysis of covariance; CEMA = 2-cyanoethylmercapturic acid; 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 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 15.2.3.4](#).

On Day 5, the LS mean of CEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 82.77% lower than that of subjects who continued to smoke mCC (95% CI: 79.45, 85.56; 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.

Data for the PP Set on Day 90 are presented in [Table 89](#).

**Table 89 Analysis of CEMA versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		95% CI
				(THS m2.2:mCC)	CV (%)	
Quantity excreted over 24 hours (µg)	THS m2.2	45	20.54	15.23	126.86	9.52, 24.36
	mCC	29	134.84			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	43	11.88	14.29	121.48	9.01, 22.67
	mCC	29	83.10			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		95% CI
				(THS m2.2:SA)	CV (%)	
Quantity excreted over 24 hours (µg)	THS m2.2	45	20.54	86.88	126.86	42.19, 178.88
	SA	9	23.64			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	43	11.88	82.18	121.48	40.63, 166.22
	SA	9	14.45			

Abbreviations: ANCOVA = analysis of covariance; CEMA = 2-cyanoethylmercapturic acid; 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 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 15.2.3.4](#).

On Day 90, the LS mean of CEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 85.71% lower than that of subjects who continued to smoke mCC (95% CI: 77.33, 90.99; 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%.

The sensitivity analysis on the Compliant Population and the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS mean of CEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 40.74% lower than that of subjects who abstained from smoking (95% CI: 11.41, 60.36).

#### 11.2.3.9 2-hydroxyethyl mercapturic acid in 24-hour Urine During the Study

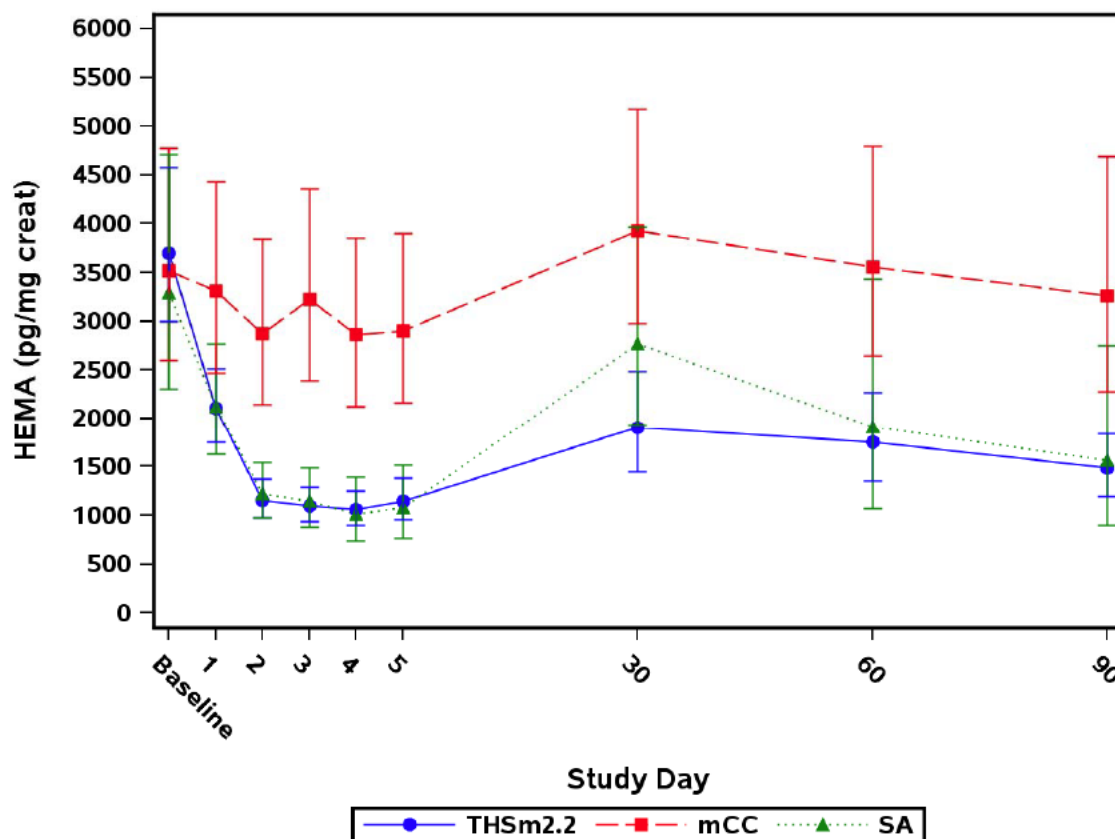
Subject listings of HEMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of HEMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided together with percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 17](#).





**Figure 17 Geometric Mean and 95% CI HEMA Urinary 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 was the last assessment prior to first 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2.](#)

The profile of HEMA for the THS 2.2 Menthol arm was comparable to that of the SA arm, with a gradual decline from baseline to Day 2 before plateauing during the remainder of the Confinement Period. Geometric mean HEMA values decreased in the THS 2.2 Menthol arm from baseline (3702.58 pg/mg creat) to Day 5 (1145.34 pg/mg creat), whereas HEMA in the mCC arm decreased but to a lesser extent from a baseline of 3520.78 pg/mg creat to 2903.31 pg/mg creat on Day 5. These values corresponded to percent changes from baseline of -62.69% and -7.74% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean HEMA values decreased from



baseline (3289.73 pg/mg creat) to Day 5 (1075.28 pg/mg creat), as expected, which corresponded to a -62.03% change from baseline.

During the Ambulatory Period, HEMA remained reduced from baseline but was higher than the Day 5 value for the THS 2.2 Menthol arm and markedly higher than the Day 5 value for the SA arm. The HEMA values then decreased to Day 60 and Day 90, with changes from baseline of -53.06% and -9.84%, respectively, on Day 90. The decrease from baseline in the SA arm was lower than expected as the mean value is skewed by outliers, so the median decrease from baseline of -50.76% is a more accurate measure of the change from baseline for the SA arm. HEMA in the mCC arm was higher than baseline on Day 30 and gradually decreased for the remainder of the Ambulatory Period, with a change from baseline of 13.40% reported on Day 90.

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 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 on Day 5 are presented in [Table 90](#).

**Table 90 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) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	1908.19	38.67	55.19	30.99, 48.25
	mCC	31	4934.43			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	1160.03	39.19	55.70	31.22, 49.20
	mCC	30	2959.77			

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	1908.19	104.07	55.19	81.01, 133.71
	SA	22	1833.48			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	67	1160.03	104.63	55.70	80.79, 135.51
	SA	21	1108.86			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; HEMA = 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 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 15.2.3.4](#).

On Day 5, the LS mean of HEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 60.81% lower than that of subjects who continued to smoke mCC (95% CI: 50.80, 68.78; 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.

Data for the PP Set on Day 90 are presented in [Table 91](#).

**Table 91 Analysis of HEMA 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	45	2319.88	39.47	70.42		29.07, 53.59
	mCC	29	5877.88				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	1394.63	38.49	70.07		28.28, 52.38
	mCC	29	3623.38				

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	45	2319.88	78.82	70.42		49.32, 125.96
	SA	9	2943.13				
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	1394.63	77.74	70.07		48.68, 124.14
	SA	9	1793.97				

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; HEMA = 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 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 15.2.3.4](#).

On Day 90, the LS mean of HEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 61.51% lower than that of subjects who continued to smoke mCC (95% CI: 47.62, 71.72; 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%.

The sensitivity analysis on the Compliant Population and the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, the LS mean of HEMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 29.84% lower than that of subjects who abstained from smoking (95% CI: 7.56, 46.75).

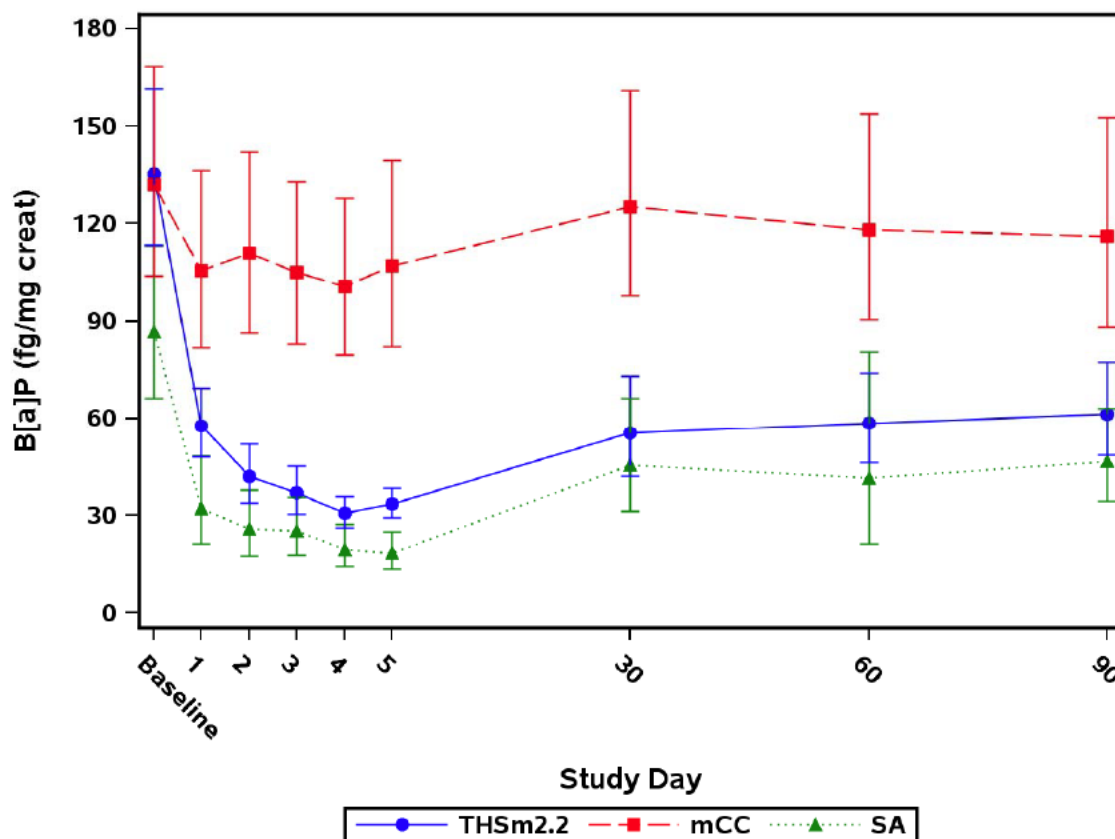
#### 11.2.3.10 3-hydroxybenzo(a)pyrene in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 18](#).



**Figure 18 Geometric Mean and 95% CI B[a]P Urinary 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 was the last assessment prior to first 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 was 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 arm was comparable to that of the SA arm, with the majority of the decrease from baseline observed on Day 1 and a further gradual decrease observed from Day 2 to Day 5. Geometric mean B[a]P values decreased in the THS 2.2 Menthol arm from baseline (135.23 fg/mg creat) to Day 5 (33.44 fg/mg creat), whereas B[a]P in the mCC arm decreased but to a lesser extent from a baseline of 132.19 fg/mg creat to 107.09 fg/mg creat on Day 5. These values corresponded to percent changes from baseline of -68.31% and -8.68% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean B[a]P values decreased from baseline



(86.69 fg/mg creat) to Day 5 (18.34 fg/mg creat), as expected, which corresponded to a -75.41% change from baseline.

During the Ambulatory Period, B[a]P remained reduced from baseline but higher than Day 5 values for the THS 2.2 Menthol and SA study arms, with changes from baseline of -50.86% and -41.82%, respectively, on Day 90. In contrast, B[a]P in the mCC arm was comparable to baseline on Day 30 and remained relatively stable for the remainder of the Ambulatory Period, with a change from baseline of 18.37% observed on Day 90.

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 on Day 5 are presented in [Table 92](#).

**Table 92 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		95% CI
				(THS m2.2:mCC) (%)	CV (%)	
Quantity excreted over 24 hours (pg)	THS m2.2	69	54.24	29.58	53.63	23.77, 36.81
	mCC	30	183.37			
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	67	32.09	28.94	54.77	23.14, 36.20
	mCC	30	110.89			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		95% CI
				(THS m2.2:SA) (%)	CV (%)	
Quantity excreted over 24 hours (pg)	THS m2.2	69	54.24	160.48	53.63	123.78, 208.04
	SA	21	33.80			
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	67	32.09	152.32	54.77	116.94, 198.39
	SA	21	21.07			

Abbreviations: ANCOVA = analysis of covariance; B[a]P = 3-hydroxybenzo(a)pyrene; 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 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 15.2.3.4.](#)

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 71.06% lower than that of subjects who continued to smoke mCC (95% CI: 63.80, 76.86; 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 mean of B[a]P concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 52.32% higher than that of subjects who abstained from smoking (95% CI: 116.94, 198.39). 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.

The sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented. For the FAS, the result for the THS 2.2 Menthol versus mCC comparison was consistent with the result from the PP Set. For the THS 2.2 Menthol versus SA comparison, 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%.

Data for the PP Set on Day 90 are presented in [Table 93](#).

**Table 93 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)			95% CI
				(%)	CV (%)		
Quantity excreted over 24 hours (pg)	THS m2.2	45	91.91	45.11	71.91		32.89, 61.85
	mCC	29	203.76				
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	43	54.65	43.33	71.37		31.52, 59.57
	mCC	29	126.12				

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA)			95% CI
				(%)	CV (%)		
Quantity excreted over 24 hours (pg)	THS m2.2	45	91.91	96.05	71.91		58.84, 156.78
	SA	9	95.69				
Concentration adjusted for creatinine (fg/mg creat)	THS m2.2	43	54.65	92.93	71.37		57.11, 151.22
	SA	9	58.81				

Abbreviations: ANCOVA = analysis of covariance; B[a]P = 3-hydroxybenzo(a)pyrene; 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 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 15.2.3.4.](#)

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 56.67% lower than that of subjects who continued to smoke mCC (95% CI: 40.43, 68.48; 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.

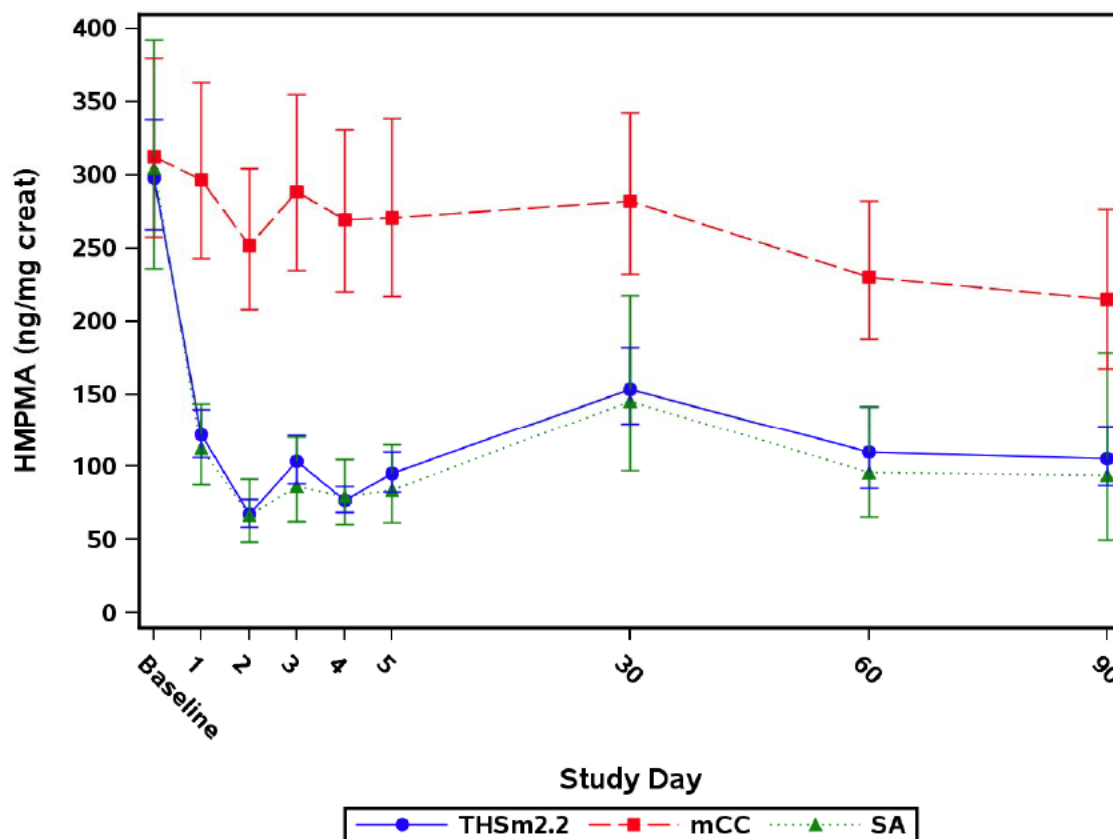
#### 11.2.3.11 3-hydroxy-1-methylpropylmercapturic acid in 24-hour Urine During Study

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 19](#).



**Figure 19 Geometric Mean and 95% CI HMPMA Urinary 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 cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was the last assessment prior to first 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 was 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 THS 2.2 Menthol arm was comparable to that of the SA arm, with the majority of the reduction achieved on Day 1 with further reduction on Day 2 and levels undulating for the remainder of the Confinement Period. Geometric mean HMPMA values decreased in the THS 2.2 Menthol arm from baseline (297.82 ng/mg creat) to Day 5 (95.35 ng/mg creat), whereas HMPMA values in the mCC arm decreased to a lesser extent from baseline (312.55 ng/mg creat) to Day 5 (270.99 ng/mg creat). These values corresponded to percent changes from baseline of -63.03% and -12.69% for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean HMPMA values decreased from baseline (304.27 ng/mg creat) to





Day 5 (84.11 ng/mg creat), as expected, which corresponded to a -68.67% change from baseline.

During the Ambulatory Period, HMPMA remained reduced from baseline but higher than Day 5 values on Day 30 before decreasing to Day 60 and Day 90 for the THS 2.2 Menthol and SA study arms, with changes from baseline of -57.41% and -52.81%, respectively, on Day 90. In contrast, HMPMA in the mCC arm was comparable to baseline on Day 30 and decreased for the remainder of the Ambulatory Period, with a change from baseline of -18.97% observed on Day 90.

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 on Day 5 are presented in [Table 94](#).

**Table 94 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	70	158.79	37.18	55.13	29.82, 46.36
	mCC	31	427.05			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	67	95.32	38.26	53.56	30.73, 47.64
	mCC	30	249.13			

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	158.79	116.62	55.13	90.86, 149.67
	SA	22	136.16			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	67	95.32	120.95	53.56	94.28, 155.18
	SA	21	78.81			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; 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 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 15.2.3.4](#).

On Day 5, the LS mean of HMPMA concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 61.74% lower than that of subjects who continued to smoke mCC (95% CI: 52.36, 69.27; 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.

Data for the PP Set on Day 90 are presented in in [Table 95](#).

**Table 95 Analysis of HMPMA 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 (µg)	THS m2.2	45	173.20	49.10	61.54	37.41, 64.42
	mCC	29	352.77			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	43	107.87	49.63	64.74	37.25, 66.13
	mCC	29	217.35			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV (%)	95% CI
				(THS m2.2:SA) (%)		
Quantity excreted over 24 hours (µg)	THS m2.2	45	173.20	99.72	61.54	65.61, 151.57
	SA	9	173.68			
Concentration adjusted for creatinine (ng/mg creat)	THS m2.2	43	107.87	102.41	64.74	66.08, 158.69
	SA	9	105.34			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variation; 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 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 15.2.3.4](#).

On Day 90, the LS mean of HMPMA concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 50.37% lower than that of subjects who continued to smoke mCC (95% CI: 33.87, 62.75; 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.

#### 11.2.3.12 S-benzylmercapturic Acid in 24-hour Urine During the Study

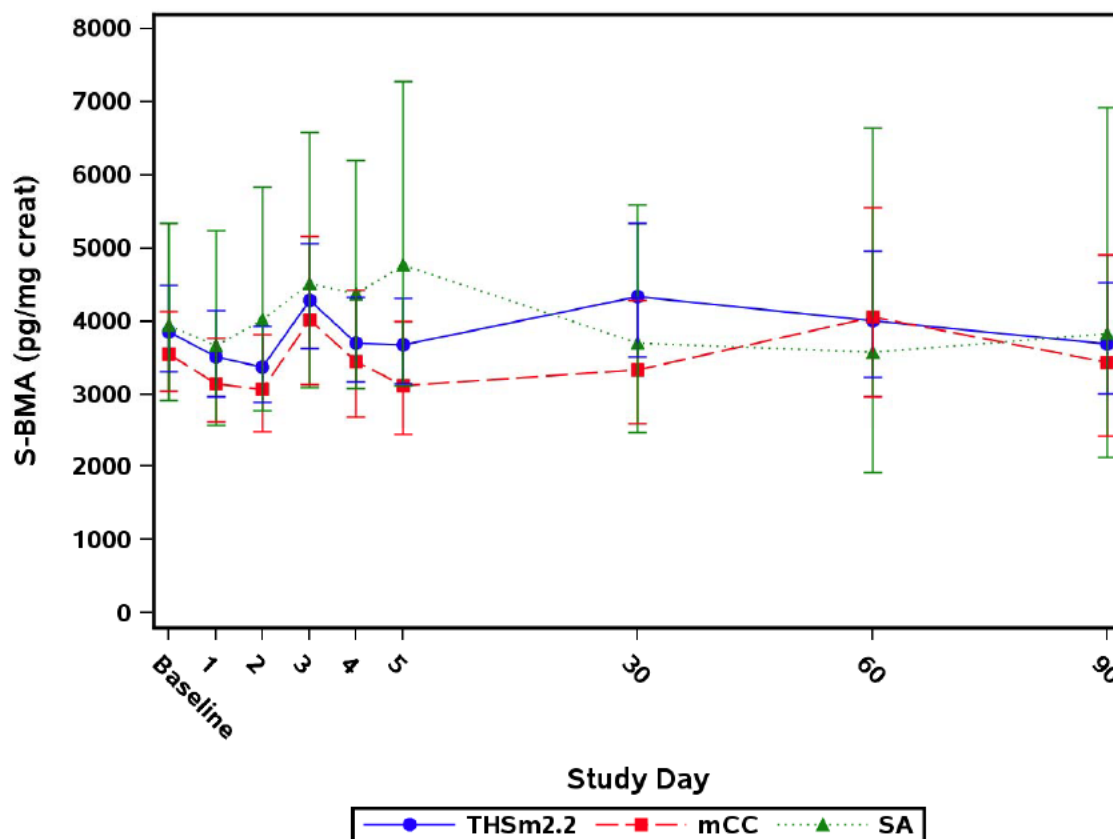
Subject listings of S-BMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

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 percent 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 FAS, respectively. Data for the PP Set are also presented in [Figure 20](#).





**Figure 20 Geometric Mean and 95% CI S-BMA 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-BMA = S-benzylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was the last assessment prior to first 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 was 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 the THS 2.2 Menthol and mCC study arms, with no evidence of any notable decrease in the THS 2.2 Menthol arm compared to the mCC arm. S-BMA values increased from baseline to Day 5 in the SA arm. Geometric mean S-BMA values in the THS 2.2 Menthol, mCC, and SA arms were 3855.95, 3549.66, and 3944.45 pg/mg creat, respectively, at baseline and 3683.79, 3120.82, and 4769.75 pg/mg creat, respectively on Day 5, which corresponded to percent changes from baseline of 9.56%, 9.69%, and 38.83% for the THS 2.2 Menthol, mCC, and SA arms, respectively.



During the Ambulatory Period, the profiles of mean S-BMA values were similar for all study arms and similar to baseline values.

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 on Day 5 are presented in [Table 96](#).

**Table 96 Analysis of S-BMA versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean Ratio			
			Geometric LS Mean	(THS m2.2:mCC) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	67	6326.41	117.21	63.23	90.89, 151.13
	mCC	30	5397.72			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	65	3745.43	116.05	62.06	90.29, 149.14
	mCC	30	3227.50			

Parameter	Exposure	Number of Subjects	Geometric LS Mean Ratio			
			Geometric LS Mean	(THS m2.2:SA) (%)	CV (%)	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	67	6326.41	81.78	63.23	61.34, 109.03
	SA	21	7735.76			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	65	3745.43	81.01	62.06	60.97, 107.63
	SA	21	4623.62			

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; 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 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 15.2.3.4](#).



On Day 5, the LS means of both S-BMA 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 continued to smoke mCC, with 95% CIs for both assessments spanning 100%.

On Day 5, the LS means of both S-BMA 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 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.

Data for the PP Set on Day 90 are presented in [Table 97](#).

**Table 97 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		95% CI
				(THS m2.2:mCC) (%)	CV (%)	
Quantity excreted over 24 hours (ng)	THS m2.2	45	6075.93	107.00	88.16	74.29, 154.10
	mCC	29	5678.61			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	3793.16	109.86	91.35	75.25, 160.39
	mCC	29	3452.68			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		95% CI
				(THS m2.2:SA) (%)	CV (%)	
Quantity excreted over 24 hours (ng)	THS m2.2	45	6075.93	82.87	88.16	47.10, 145.77
	SA	9	7332.21			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	43	3793.16	88.13	91.35	49.39, 157.24
	SA	9	4304.05			

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; 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 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 15.2.3.4.](#)

On Day 5, the LS means of both S-BMA 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 continued to smoke mCC, with 95% CIs for both assessments spanning 100%.

On Day 5, the LS means of both S-BMA 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 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.

#### 11.2.4 Biomarkers of Exposure to Nicotine During the Study

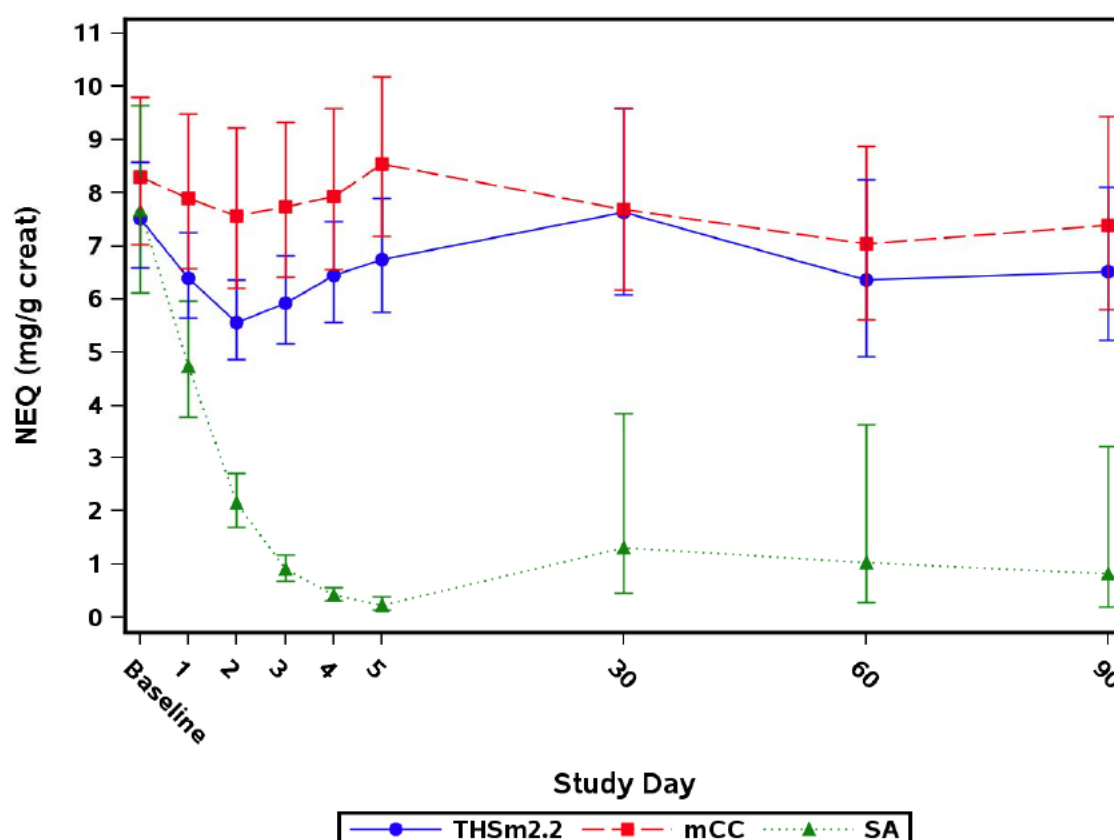
##### 11.2.4.1 Nicotine Equivalents in 24-hour Urine During the Study

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 percent 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 FAS, respectively. Data for the PP Set are also provided in [Figure 21](#).



**Figure 21 Geometric Mean and 95% CI Urinary NEQ Quantity Adjusted for Creatinine During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; NEQ = nicotine equivalents; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was the last assessment prior to first 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.1.2](#).

In the mCC arm, mean NEQ values remained similar to baseline throughout the Confinement Period, whereas NEQ values in the THS 2.2 Menthol arm decreased from baseline to Day 2 before increasing gradually for the remainder of the Confinement Period. In the SA arm, NEQ levels steadily decreased from Day 1 to Day 5. Geometric mean NEQ values at baseline and Day 5 were 7.52 and 6.74 mg/g creat, respectively, for the THS 2.2 Menthol arm, and 8.30 and 8.55 mg/g creat, respectively, for the mCC arm. These values corresponded to percent changes from baseline of -1.77% and 6.02%, for the THS 2.2 Menthol and mCC respectively. In the SA arm, geometric mean NEQ values decreased from baseline (7.68 mg/g creat) to Day 5 (0.23 mg/g creat), as expected, corresponding to a -92.74% change from baseline.



During the Ambulatory Period, mean NEQ values were comparable to baseline on Day 30 for the THS 2.2 Menthol and mCC arm before decreasing moderately on Days 60 and 90. The percent changes from baseline on Days 30, 60, and 90 were 6.60%, -1.39%, and -3.86% for the THS 2.2 Menthol arm, respectively, and 2.77%, -4.48%, and -4.24% for the mCC arm, respectively. In the SA arm, NEQ values remained decreased from baseline but higher than the Day 5 value on Day 30 before decreasing moderately on Days 60 and 90, with a mean of 0.82 mg/g creat on Day 90 (-63.38% change from baseline).

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 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 THS 2.2 Menthol versus mCC for the PP Set on Day 5 are presented in [Table 98](#).

**Table 98 Analysis of NEQ versus mCC on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio Geometric(THS m2.2:mCC) CV (%) (%) 95% CI		
Quantity excreted over 24 hours (mg)	THS m2.2	69	11.41	84.24	60.15	66.33, 106.97
	mCC	31	13.54			
Concentration adjusted for creatinine (mg/g creat)	THS m2.2	67	7.06	87.33	52.06	70.49, 108.18
	mCC	30	8.08			

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 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 15.2.3.4](#).

On Day 5, the LS means of both NEQ urinary concentration adjusted for creatinine and quantity excreted over 24 hours was 12.67% and 15.74% lower respectively in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC, although the 95% CIs spanned 100% (-8.18, 29.51 and -6.97, 33.67 , respectively).



Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.

Data for the PP Set on Day 90 are presented in [Table 99](#).

**Table 99 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	44	10.61	94.96	89.00	65.61, 137.45
	mCC	29	11.18			
Concentration adjusted for creatinine (mg/g creat)	THS m2.2	43	6.59	96.30	89.23	66.43, 139.59
	mCC	29	6.84			

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 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 15.2.3.4](#).

On Day 90, no notable differences were observed for either NEQ urinary concentration adjusted for creatinine or 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

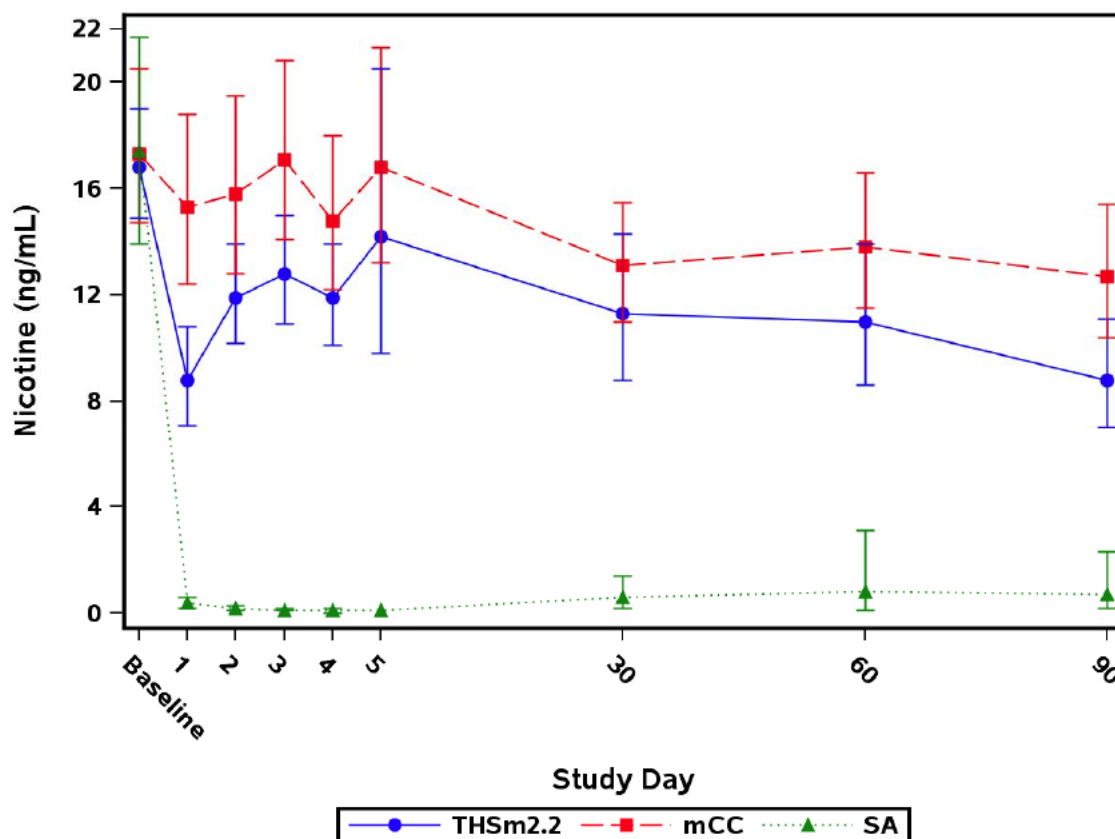
Plasma nicotine concentrations (ng/mL) and sampling times are listed by subject in [Appendix 15, Listing 15.3.3.3](#). Plasma nicotine concentrations are summarized by study arm in [Appendix 15, Table 15.2.4.19.1](#) and [Table 15.2.4.19.2](#) for the PP Set and FAS, respectively.





Geometric mean and 95% CIs concentrations are shown by study arm in [Appendix 15](#), [Figure 15.1.2.1.1](#) and [Figure 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 interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15](#), [Figure 15.1.2.1.1](#).

The geometric mean plasma nicotine concentration profile for samples taken between 08:00 and 09:30 PM in the mCC arm showed levels fluctuated during the Confinement Period but levels were comparable to baseline (17.32 ng/mL) at T0 + 14h on Day 5 (16.77 ng/mL). In the THS 2.2 Menthol arm, nicotine concentrations dropped from baseline (16.84 ng/mL) to Day 1 (8.78 ng/mL) before steadily increasing for the remainder of the Confinement Period and had reached 14.23 ng/mL at T0 + 14h on



Day 5. In the SA arm, the mean nicotine concentration was comparable to the other study arms at baseline (17.39 ng/mL) before decreasing sharply to 0.39 ng/mL on Day 1, where concentrations remained decreased for the remainder of the Confinement Period. The number (percentage) of below the limit of quantification (BLOQ) values for the SA arm increased from 4 subjects (17.4%) on Day 1 to all subjects by Day 5.

During the Ambulatory Period, geometric mean nicotine concentrations on Day 30 were decreased from baseline values for the THS 2.2 Menthol and mCC arms, with the decrease continuing for the THS 2.2 Menthol arm. On Day 90 geometric mean nicotine concentrations were 8.82 ng/mL and 12.65 ng/mL for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean nicotine concentration had increased from the Day 5 value (all values were BLOQ) on Day 30 (0.57 ng/mL) and increased to 0.76 and 0.74 ng/mL on Days 60 and 90, respectively.

Analysis of the plasma nicotine concentrations during the study is presented in [Appendix 15](#), [Table 15.2.4.20.1](#) and [Table 15.2.4.20.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 100](#).

**Table 100 Analysis of Plasma Nicotine Concentrations (ng/mL) During the Study (PP Set)**

Exposure	Day	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC)	95% CI
				(%)	
THS m2.2	1	74	8.81	59.18	46.03, 76.09
mCC		34	14.88		
THS m2.2	2	74	11.75	76.94	62.67, 94.47
mCC		34	15.27		
THS m2.2	3	74	12.60	76.03	61.54, 93.94
mCC		33	16.57		
THS m2.2	4	74	11.85	81.61	66.89, 99.57
mCC		34	14.52		
THS m2.2	5	69	14.07	79.69	65.75, 96.57
mCC		34	17.65		
THS m2.2	30	39	11.99	91.90	65.28, 129.36
mCC		33	13.05		
THS m2.2	60	39	11.38	86.41	56.84, 131.37
mCC		33	13.17		
THS m2.2	90	47	8.93	71.98	51.13, 101.33
mCC		31	12.40		

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 an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC/CC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.20.1](#).

On Days 1 to 5, nicotine LS means concentrations were approximately 18% to 41% lower in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, with the upper limit of the 95% CIs less than 100%. However, the difference in nicotine concentration between THS 2.2 Menthol and mCC users decreased between the start and the end of the Confinement Period.

On Days 30, 60, and 90, plasma nicotine concentrations were approximately 8%, 14%, and 28% lower in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, although the 95% CIs spanned 100%.

The results for the FAS were consistent with the results from the PP Set.



Subject listings of plasma nicotine concentration PK 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 101](#).

**Table 101 Summary of Plasma Nicotine Concentration PK Parameters on Day 5 (PP Set)**

Parameter (unit)	THS m2.2 (N=75)	mCC (N=35)
<b>C<sub>peak</sub> (ng/mL)</b>		
Number of subjects	74	34
Geometric mean	20.909	23.271
95% CI	18.621, 23.477	20.251, 26.740
Min, Max	2.34, 47.40	7.67, 43.40
CV (%)	53.2911	41.4589
<b>t<sub>peak</sub> (h)</b>		
Number of subjects	74	34
Median	15.933	14.067
Min, Max	1.97, 16.25	1.82, 16.25
<b>C<sub>avg</sub> (ng/mL)</b>		
Number of subjects	74	34
Geometric mean	11.083	12.955
95% CI	9.714, 12.645	11.289, 14.866
Min, Max	1.13, 24.45	4.65, 26.08
CV (%)	61.8249	41.0095

Abbreviations: C<sub>avg</sub> = weighted average concentration over 24 hours; CI = confidence interval; C<sub>peak</sub> = 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<sub>peak</sub> = time to peak concentration.

Data Source: [Appendix 15, Table 15.2.4.21.1](#)

Analysis of the plasma nicotine concentration PK 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 102](#).



**Table 102 Analysis of Plasma Nicotine Concentration PK Parameters on Day 5 (PP Set)**

Geometric LS Means Ratio						
Parameter (unit)	Exposure	Number of Subjects	Geometric LS Mean	(THS m2.2:mCC) (%)	CV (%)	95% CI
C <sub>avg</sub> <sup>1</sup> (ng/mL)	THS m2.2	74	11.05	85.20	56.00	68.74, 105.61
	mCC	34	12.97			
C <sub>peak</sub> <sup>1</sup> (ng/mL)	THS m2.2	74	20.96	89.46	49.68	73.75, 108.51
	mCC	34	23.43			

Parameter (unit)	Exposure	Number of Subjects	Median (h)	Median Difference (h)	95% CI
t <sub>peak</sub> <sup>2</sup> (h)	THS m2.2	74	14.97	0.18	0.00, 1.94
	mCC	34	13.03		

Abbreviations: C<sub>avg</sub> = weighted average concentration over 24 hours; CI = confidence interval; C<sub>peak</sub> = 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<sub>peak</sub> = time to peak concentration.

<sup>1</sup> Geometric LS mean and 95% CI are the adjusted geometric LS means based on an ANCOVA 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.

<sup>2</sup> 95% CIs 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, weighted average and peak plasma concentrations were approximately 15% and 11% lower for the THS 2.2 Menthol arm compared to mCC arm, respectively, although the 95% CIs spanned 100%. The median t<sub>peak</sub> on Day 5 was 0.18 hours later for the THS 2.2 Menthol arm compared to the mCC arm (95% CI: 0.00, 1.94).

The results for the FAS were consistent with the results from the PP Set.

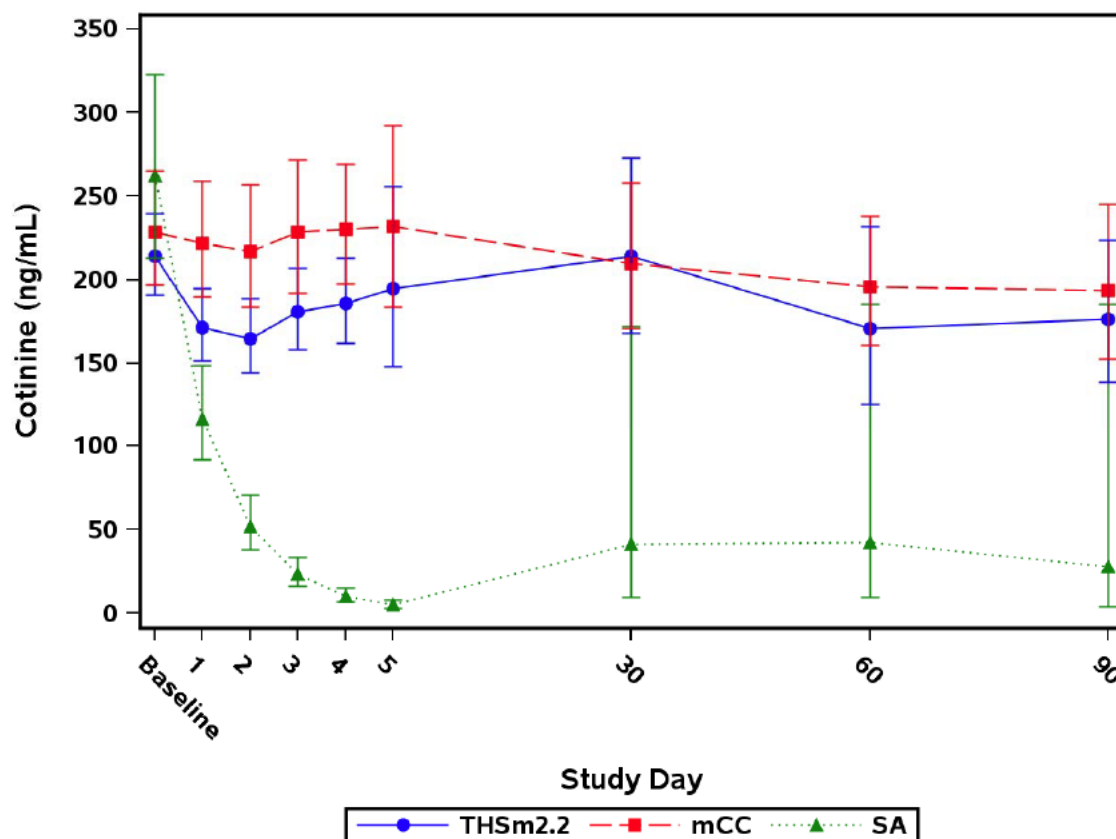
#### 11.2.4.2.2 Plasma Cotinine Concentrations and PK Parameters

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 [Table 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 [Figure 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 interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15](#), [Figure 15.1.2.1.1](#).

The geometric mean plasma cotinine concentration profile for samples taken between 08:00 and 09:30 PM in the mCC arm showed levels were comparable to baseline (228.30 ng/mL) throughout the Confinement Period. In the THS 2.2 Menthol arm, cotinine concentrations decreased from baseline (213.94 ng/mL) to Day 2 (164.96 ng/mL) before steadily increasing for the remainder of the Confinement Period and had reached 194.68 ng/mL at T0 + 14h on Day 5. In the SA arm, the mean cotinine concentration was



comparable to the other study arms at baseline (262.31 ng/mL) and decreased steadily for the remainder of the Confinement Period, falling to 4.90 ng/mL on Day 5.

During the Ambulatory Period, geometric mean cotinine concentrations on Day 30 were comparable to baseline values for the THS 2.2 Menthol and mCC arms, with decreases in concentrations observed between Day 30 and Day 90. On Day 90 geometric mean cotinine concentrations were 176.22 ng/mL and 193.39 ng/mL for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean cotinine concentration had increased from the Day 5 value on Day 30 (40.97 ng/mL) and was 42.41 and 27.93 ng/mL on Days 60 and 90, respectively.

Analysis of the plasma cotinine concentrations during the study is presented in [Appendix 15](#), [Table 15.2.4.20.1](#) and [Table 15.2.4.20.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Table 103](#).

**Table 103 Analysis of Plasma Cotinine Concentrations (ng/mL) During the Study (PP Set)**

Exposure	Day	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC)	95% CI
				(%)	
THS m2.2	1	74	179.48	82.74	74.67, 91.69
mCC		34	216.91		
THS m2.2	2	74	172.00	81.41	71.47, 92.74
mCC		34	211.27		
THS m2.2	3	74	187.97	84.58	72.51, 98.65
mCC		33	222.25		
THS m2.2	4	74	193.27	86.30	72.59, 102.60
mCC		34	223.95		
THS m2.2	5	70	192.05	84.10	72.01, 98.22
mCC		34	228.36		
THS m2.2	30	39	233.17	112.52	70.76, 178.90
mCC		33	207.23		
THS m2.2	60	39	188.85	106.19	66.77, 168.88
mCC		33	177.84		
THS m2.2	90	47	183.36	102.65	65.82, 160.08
mCC		31	178.63		

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 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.

Data Source: [Appendix 15, Table 15.2.4.20.1](#).

On Days 1 to 5, cotinine LS means concentrations were approximately 14% to 19% lower in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, with the upper limit of the 95% CIs less than 100%, except on Day 4 where the upper limit was above 100%.

On Days 30, 60, and 90, plasma cotinine concentrations were approximately 13%, 6%, and 3% higher in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, although the 95% CIs spanned 100%.

The results for the FAS were consistent with the results from the PP Set.





Subject listings of plasma cotinine concentration PK 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 104](#).

**Table 104 Summary of Plasma Cotinine Concentration PK Parameters on Day 5 (PP Set)**

Parameter (unit)	THS m2.2 (N=75)	mCC (N=35)
<b>C<sub>peak</sub> (ng/mL)</b>		
Number of subjects	74	34
Geometric mean	219.75	256.44
95% CI	197.41, 244.61	221.39, 297.03
Min, Max	30.7, 476.0	55.6, 484.0
CV (%)	48.841	44.049
<b>t<sub>peak</sub> (h)</b>		
Number of subjects	74	34
Median	16.008	16.000
Min, Max	0.00, 24.10	0.00, 20.03
<b>C<sub>avg</sub> (ng/mL)</b>		
Number of subjects	74	34
Geometric mean	190.964	233.512
95% CI	168.179, 216.837	200.992, 271.294
Min, Max	16.18, 438.03	50.87, 464.33
CV (%)	59.2347	45.0440

Abbreviations: C<sub>avg</sub> = weighted average concentration over 24 hours; CI = confidence interval; C<sub>peak</sub> = 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<sub>peak</sub> = time to peak concentration.

Data Source: [Appendix 15, Table 15.2.4.21.1](#)

Analysis of the plasma cotinine concentration PK 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 105](#).

**Table 105 Analysis of Plasma Cotinine Concentration PK Parameters on Day 5 (PP Set)**

Geometric LS Means Ratio						
Parameter (unit)	Exposure	Number of Subjects	Geometric LS Mean	(THS m2.2:mCC) (%)	CV (%)	95% CI
C <sub>avg</sub> <sup>1</sup> (ng/mL)	THS m2.2	74	189.00	81.57	55.32	65.95, 100.87
	mCC	34	231.72			
C <sub>peak</sub> <sup>1</sup> (ng/mL)	THS m2.2	74	217.64	85.36	47.36	70.95, 102.70
	mCC	34	254.96			

Median Difference						
Parameter (unit)	Exposure	Number of Subjects	Median (h)	Median Difference (h)	95% CI	
t <sub>peak</sub> <sup>2</sup> (h)	THS m2.2	74	16.07	0.03	-0.10, 1.62	
	mCC	34	16.03			

Abbreviations: C<sub>avg</sub> = weighted average concentration over 24 hours; CI = confidence interval; C<sub>peak</sub> = 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<sub>peak</sub> = time to peak concentration.

<sup>1</sup> Geometric LS mean and 95% CI are the adjusted geometric least squares means based on an ANCOVA 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.

<sup>2</sup> 95% CIs 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, weighted average and peak plasma concentrations were approximately 18% and 15% lower for the THS 2.2 Menthol arm compared to mCC arm, respectively, although the upper limit of the 95% CIs was just above 100%. The median t<sub>peak</sub> on Day 5 was approximately 16.0 hours for both the THS 2.2 Menthol and mCC arms.

The results for the FAS were consistent with the results from the PP Set, although the upper limit of the 95% CIs was less than 100% for the analysis of C<sub>peak</sub>.

#### 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 percent 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.

Percent change from baseline data for the PP Set on Day 5 are presented in [Table 106](#).

**Table 106 Descriptive Statistics of Percent Change from Baseline in CYP1A2 Activity (%) During the Confinement Period (PP Set)**

Study Arm	Time Point	Number		Arithmetic Mean	SD	Min	Median	Max
		of Subjects						
THS m2.2	Day 5 % change from baseline	74		-32.813	16.7847	-69.22	-33.716	24.98
mCC	Day 5 % change from baseline	34		3.556	13.4029	-17.97	3.281	39.24
SA	Day 5 % change from baseline	23		-34.532	11.7910	-54.92	-35.519	-19.38

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. % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm. Data Source: [Appendix 15, Table 15.2.4.23.1](#).

At baseline, CYP1A2 activity was similar between study arms, with geometric mean values of 117.595%, 121.602%, and 114.031% for the THS 2.2 Menthol, mCC, and SA arms, respectively. In the THS 2.2 Menthol and SA arms, CYP1A2 activity decreased by 32.81% and 34.53%, respectively, on Day 5. In the mCC arm, CYP1A2 activity increased by 3.56%. Comparable changes from baseline were observed when subject assessments with concomitant medication affecting CYP1A2 activity were excluded. This affected 7, 1, and 0 subjects in the THS 2.2 Menthol, mCC, and SA arms, respectively, on Day 5.

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. In addition, analyses excluding any assessments taken within 5 half-lives of a concomitant medication known to impact CYP1A2 activity are presented in [Appendix 15, Table 15.2.4.24.1.1](#) and [15.2.4.24.2.1](#) for the PP Set and FAS, respectively.



Data for the PP Set on Day 5 are presented in [Table 107](#).

**Table 107 Analysis of CYP1A2 Activity (%) versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio	CV (%)	95% CI
				(THS m2.2:mCC) (%)		
CYP1A2 activity (%)	THS m2.2	74	75.784	63.52	20.74	58.34, 69.17
	mCC	33	119.300			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio	CV (%)	95% CI
				(THS m2.2:SA) (%)		
CYP1A2 activity (%)	THS m2.2	74	75.784	101.54	20.74	92.14, 111.89
	SA	23	74.635			

Abbreviations: 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 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 15.2.4.24.1](#)

On Day 5, the LS means of CYP1A2 activity following THS 2.2 Menthol use was 36.48% lower than in subjects who continued to smoke mCC (95% CI: 30.83, 41.66; p-value <0.001).

There was no notable difference for CYP1A2 activity on Day 5 between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for the ratio of LS means spanning 100%.

The results from the FAS and the analysis excluding subject assessments with concomitant medication affecting CYP1A2 activity were comparable to the results presented above.

Percent change from baseline data for the PP Set on Day 90 are presented in [Table 108](#).



**Table 108 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	47	-31.955	28.7852	-78.97	-37.803	83.27
mCC	Day 90 % change from baseline	31	-16.706	19.5223	-45.78	-18.172	29.81
SA	Day 90 % change from baseline	9	-35.359	23.5680	-71.32	-32.907	2.63

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. % change from baseline, where baseline was 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 15.2.4.23.1](#)

At baseline, CYP1A2 activity was similar between the THS 2.2 Menthol and mCC study arms and higher in the SA arm, with mean values of 114.203%, 118.520%, and 140.462% 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 31.96% and 35.36%, respectively on Day 90. In the mCC arm, CYP1A2 activity decreased by 16.71%.

The analysis excluding assessments within 5 half-lives of concomitant medications that impact CYP1A2 activity showed consistent results, with only 2 subjects excluded from the THS 2.2 Menthol arm. Results for the FAS were consistent with the results from the PP Set for the THS 2.2 Menthol and mCC arms, but the decrease from baseline was lower for the SA arm, with a reduction of 19.163% reported.

Analyses of CYP1A2 activity on Day 90 for the PP Set are also provided in [Table 109](#).

**Table 109 Analysis of CYP1A2 Activity (%) versus mCC and SA on Day 90 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio	CV (%)	95% CI
				(THS m2.2: mCC) (%)		
CYP1A2 activity (%)	THS m2.2	47	74.308	78.57	36.81	66.36, 93.02
	mCC	30	94.574			

Parameter	Exposure	Number of Subjects	LS Mean	Geometric LS Means Ratio	CV (%)	95% CI
				(THS m2.2: SA) (%)		
CYP1A2 activity (%)	THS m2.2	47	74.308	105.34	36.81	80.49, 137.86
	SA	9	70.539			

Abbreviations: 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 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 15.2.4.24.1](#)

On Day 90, the LS means of CYP1A2 activity following THS 2.2 Menthol use was 21.43% lower than in subjects who continued to smoke mCC (95% CI: 6.98, 33.64; p-value <0.001). The FAS and the analysis excluding subject assessments with any concomitant medication within 5 half-lives known to affect CYP1A2 showed consistent results to those presented above.

The LS means of CYP1A2 were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Day 90, with the 95% CIs spanning 100%. The analysis excluding subject assessments with any concomitant medication within 5 half-lives known to affect CYP1A2 showed consistent results to those presented above. For the FAS, the LS means of CYP1A2 activity following THS 2.2 Menthol use was 15.78% lower than in subjects who abstained from smoking (95% CI: 1.14, 28.25).

### 11.2.5 Product Consumption During the Study

Details of the subjects' daily consumption of mCC during the Confinement Period are presented 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 presented in [Appendix 15, Listing 15.3.2.1.2](#). Details of product usage during the Ambulatory Period are presented in [Appendix 15, Listing 15.3.2.1.3](#).

Descriptive statistics of 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.

Details of subjects' tobacco consumption during the Ambulatory Period are presented in [Section 10.5](#) and [Section 10.6](#).

## 11.2.6 Analysis of Risk Markers During the Study

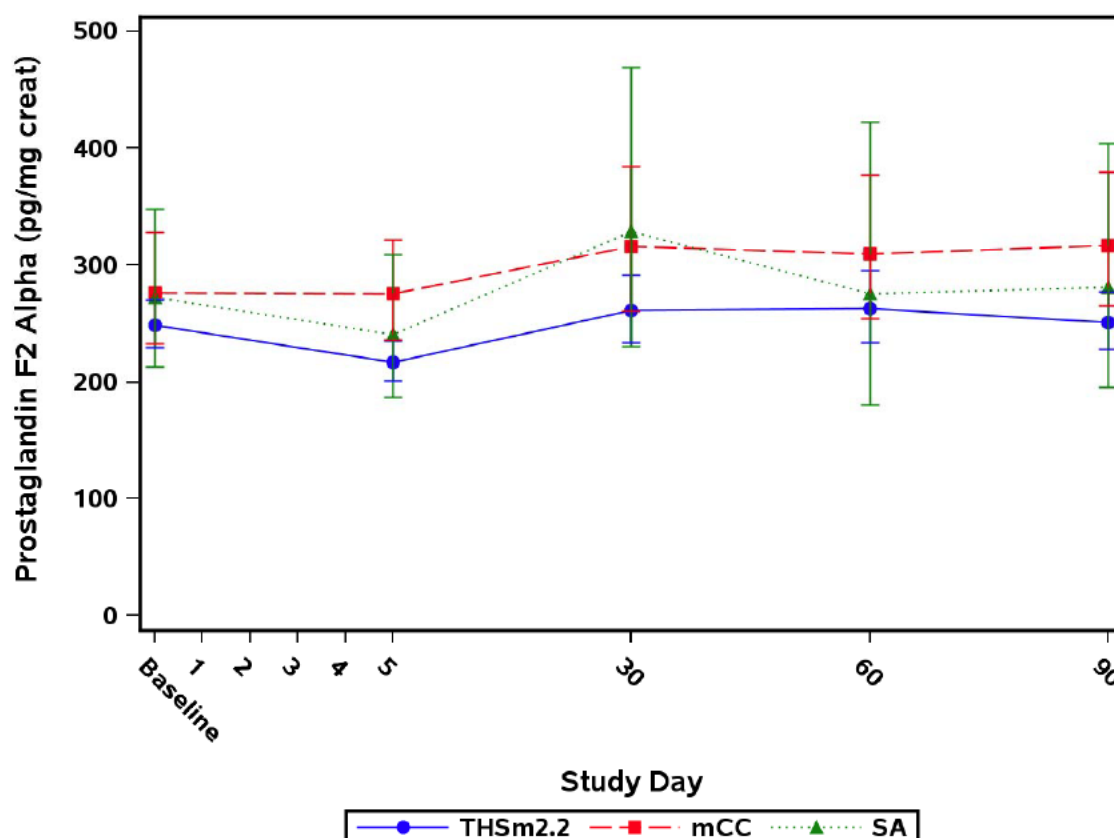
### 11.2.6.1 Risk Marker of Oxidative Stress: 8-epi-prostaglandine $F_{2\alpha}$ in 24-hour Urine (Concentration Adjusted for Creatinine) During the Study

Subject listings of 8-epi-PGF<sub>2 $\alpha$</sub>  data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of the urinary concentration of 8-epi-PGF<sub>2 $\alpha$</sub>  adjusted for creatinine during the study are provided in [Appendix 15, Table 15.2.4.32.1](#) together with percent changes from baseline. The results are also presented graphically in [Figure 24](#) and in [Appendix 15, Figure 15.1.2.3.1](#).



**Figure 24 Geometric Mean and 95% CIs 8-epi-PGF<sub>2α</sub> (pg/mg creat) During the Course of the Study (PP Set)**



Abbreviations: 8-epi-PGF<sub>2α</sub> = prostaglandin F2 alpha; CI = confidence interval; 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 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 was 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 geometric mean concentration of 8-epi-PGF<sub>2α</sub> adjusted for creatinine was 249.1, 276.4, and 272.4 pg/mg creat, respectively, in the THS 2.2 Menthol, mCC, and SA arms. On Day 5, the 8-epi-PGF<sub>2α</sub> adjusted for creatinine geometric mean values were 217.5, 275.7, and 240.6 pg/mg creat, with median percent changes from baseline of approximately -10.5%, -4.1%, and -8.9% in the THS 2.2 Menthol, mCC, and SA arms, respectively.

During the Ambulatory Period, 8-epi-PGF<sub>2α</sub> returned to approximate baseline value for the THS 2.2 Menthol arm, with median percent changes from baseline of 8.4%, 6.5%, and 1.4% for Days 30, 60, and 90, respectively. For the mCC and SA arms increases from



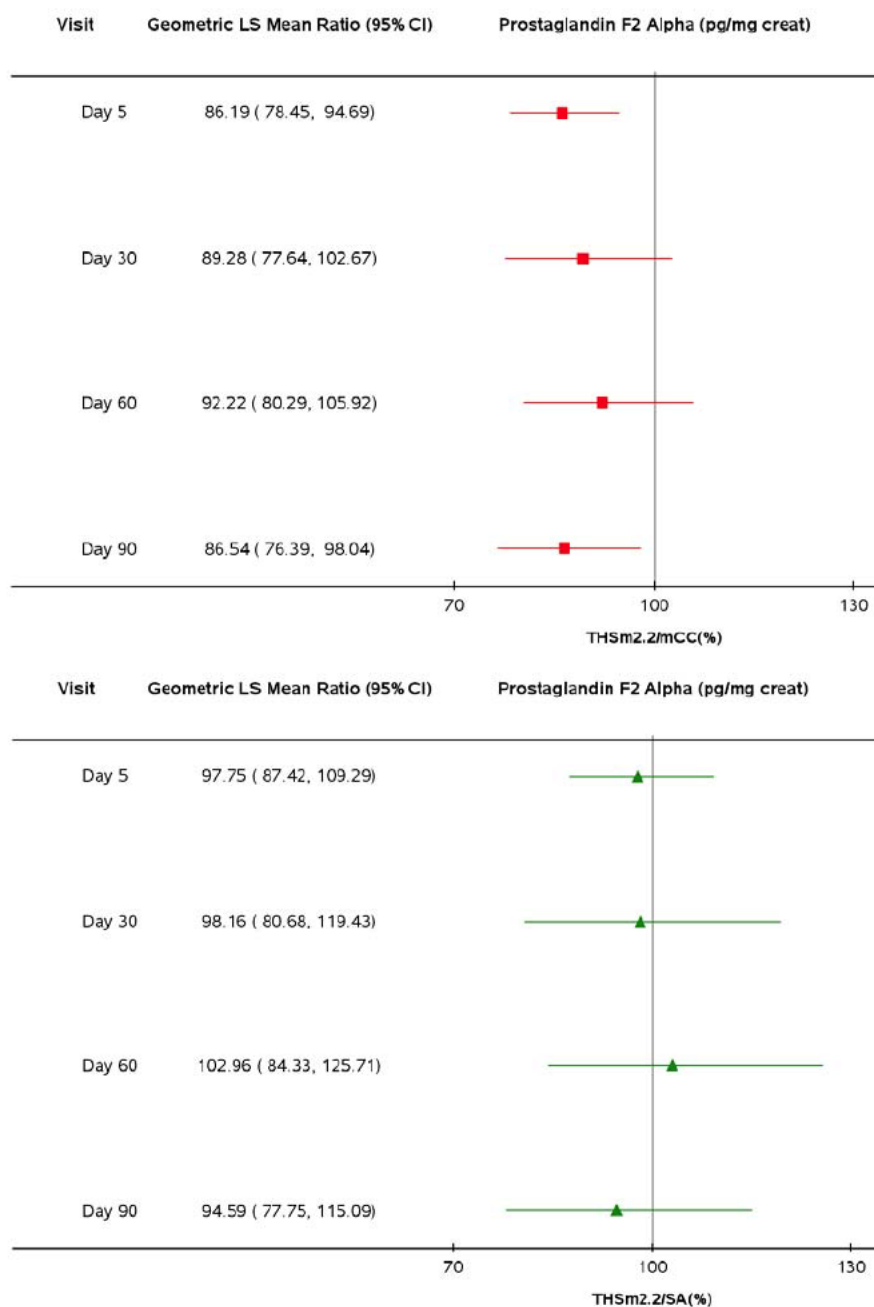


baseline were observed on Day 30. Levels of 8-epi-PGF<sub>2α</sub> then remained stable in the mCC arm on Days 60 and 90 while levels in the SA arm returned to approximate baseline value, with median percent changes of 12.9% and -1.5% on Day 90 for the mCC and SA arms, respectively.

Analyses of 8-epi-PGF<sub>2α</sub> urinary concentration adjusted for creatinine for THS 2.2 Menthol use versus mCC use and SA during the study are presented 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 are also presented graphically in [Figure 25 \(Appendix 15, Figure 15.1.2.2\)](#).



**Figure 25 Forest Plot of Statistical Analysis of 8-epi-PGF<sub>2α</sub> (pg/mg creat) During the Course of the Study (PP Set)**



Abbreviations: 8-epi-PGF<sub>2α</sub> = prostaglandin F2 alpha; CI = confidence interval; 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 8-epi-PGF<sub>2α</sub> urinary concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use was notably lower (13.81%) than that observed with subjects who continued to smoke mCC, with 95% CIs excluding 100%. During the Ambulatory Period on Days 30 and 90 the LS means of 8-epi-PGF<sub>2α</sub> urinary concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use were notably lower (10.72% and 13.46%, respectively) than those observed with subjects who continued to smoke mCC, with 95% CIs excluding 100% on Day 90. There was no notable difference between subjects who switched to THS 2.2 Menthol use and mCC use on Day 60.

On Day 5 and during the Ambulatory Period on Days 30, 60, and 90, there were no notable differences observed in 8-epi-PGF<sub>2α</sub> urinary 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%.

The results for the FAS were consistent with the results for the PP Set.

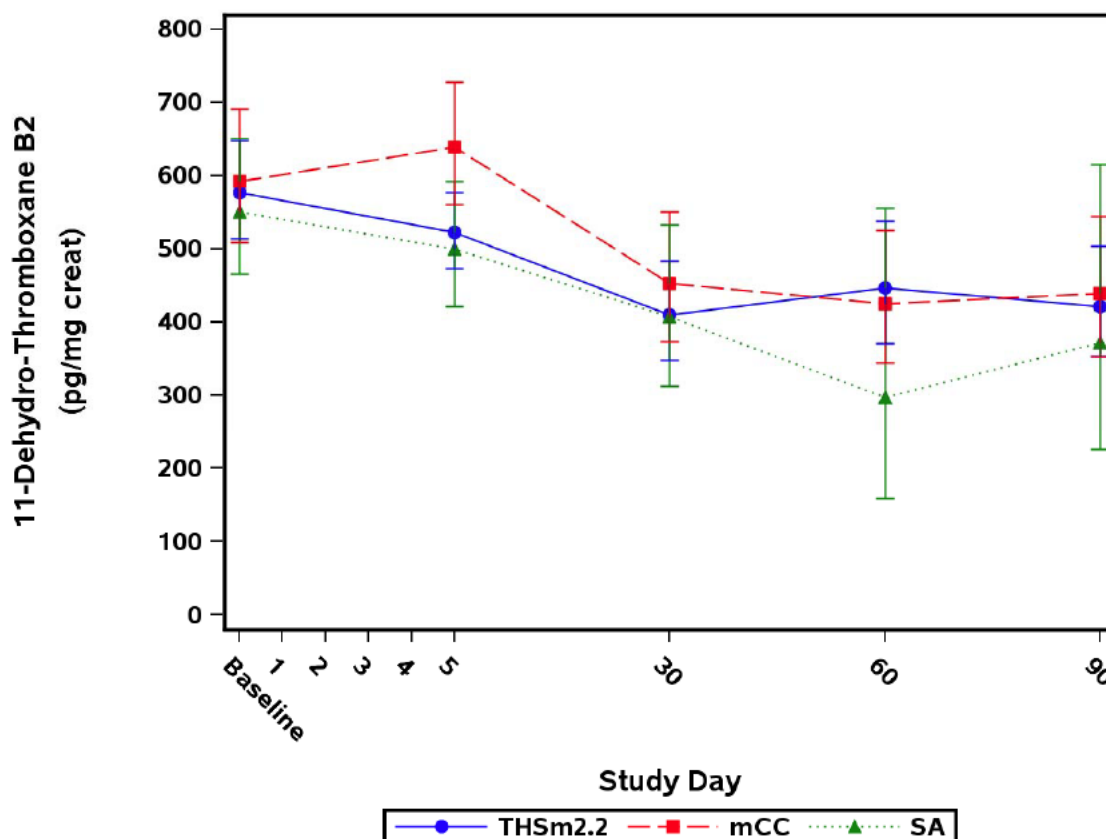
#### 11.2.6.2 Risk Marker of Platelet Activation: 11-dehydrothromboxane B2 in 24-hour Urine (Concentration Adjusted for Creatinine) During the Study

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 during the study are provided in [Appendix 15, Table 15.2.4.32.1](#) together with percent changes from baseline. The results are also presented graphically in [Figure 26](#) and in [Appendix 15, Figure 15.1.2.3.1](#).



**Figure 26 Geometric Mean and 95% CIs 11-DTX-B2 (pg/mg creat) During the Course of the Study (PP Set)**



Abbreviations: 11-DTX-B2 = 11-dehydro-thromboxane B2; CI = confidence interval; 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 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 was 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 geometric mean concentrations of 11-DTX-B2 adjusted for creatinine were 576.5, 592.6, and 550.0 pg/mg creat, for the THS 2.2 Menthol, mCC, and SA arms respectively. On Day 5, levels had decreased in the THS 2.2 Menthol and SA arms, with 11-DTX-B2 adjusted for creatinine geometric mean values of 522.4, 638.8, and 499.3 pg/mg creat (median percent changes from baseline of approximately -10.4%, 0.9%, and -8.3%) in the THS 2.2 Menthol, mCC, and SA arms, respectively.

During the Ambulatory Period, mean 11-DTX-B2 values in the THS 2.2 Menthol arm continued to decrease from Day 5 to Day 30 and remained stable for the remainder of the Ambulatory Period, with median changes from baseline on Days 30, 60, and 90 of -



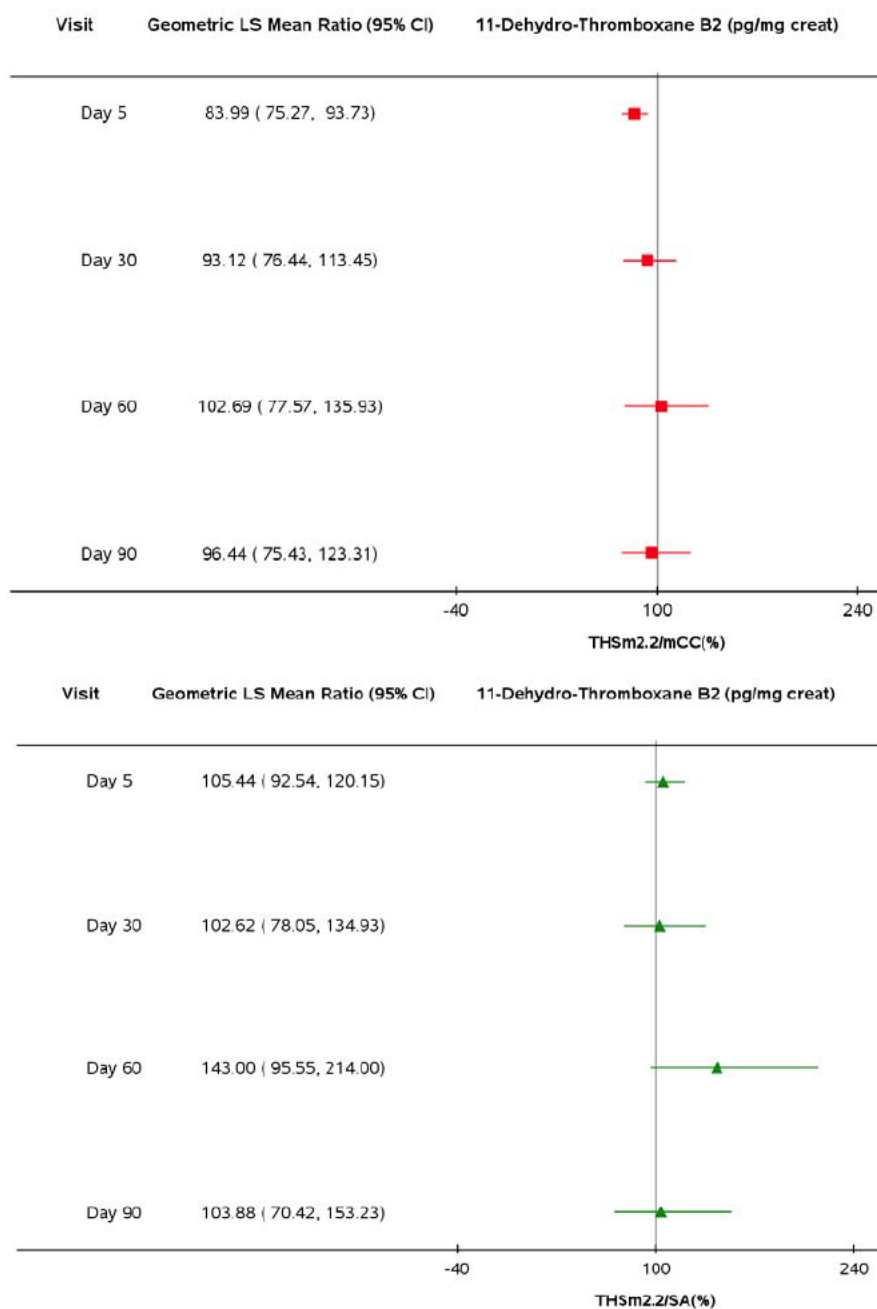


25.2%, -23.0%, and -22.0%. Mean levels of 11-DTX-B2 decreased in the mCC and SA arms from Day 5 to Day 60, before increasing moderately on Day 90, resulting in median changes from baseline of -14.2% and -22.1% on Day 90 for the mCC and SA arms, respectively.

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. In addition, statistical analyses and descriptive statistics for 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 15.2.4.32.1.1](#) for the PP Set. The analyses are also presented graphically in [Figure 27](#) ([Appendix 15, Figure 15.1.2.2](#)).



**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 interval; 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 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 16.01% lower than that of subjects who continued to smoke mCC (95% CI: 6.27, 24.73). There were no notable differences between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC during the Ambulatory Period, with the 95% CIs for the LS mean ratio spanning 100%.

On Day 5, there were no notable differences observed in 11-DTX-B2 urinary concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for the LS mean ratio spanning 100%. During the Ambulatory Period, there were no notable differences observed in 11-DTX-B2 urinary concentration adjusted for creatinine between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Day 30 and Day 90, with the 95% CIs for both assessments spanning 100%. On Day 60, the LS mean of 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 43.00% higher than that of subjects who abstained from smoking, although the 95% CIs included 100% (95% CI: 95.55, 214.00).

The results for the FAS were consistent with the results for the PP Set with the exception of the comparison between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Day 60, where no notable difference was observed between study arms.

The results for the 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 were consistent with the results for the PP Set and FAS.

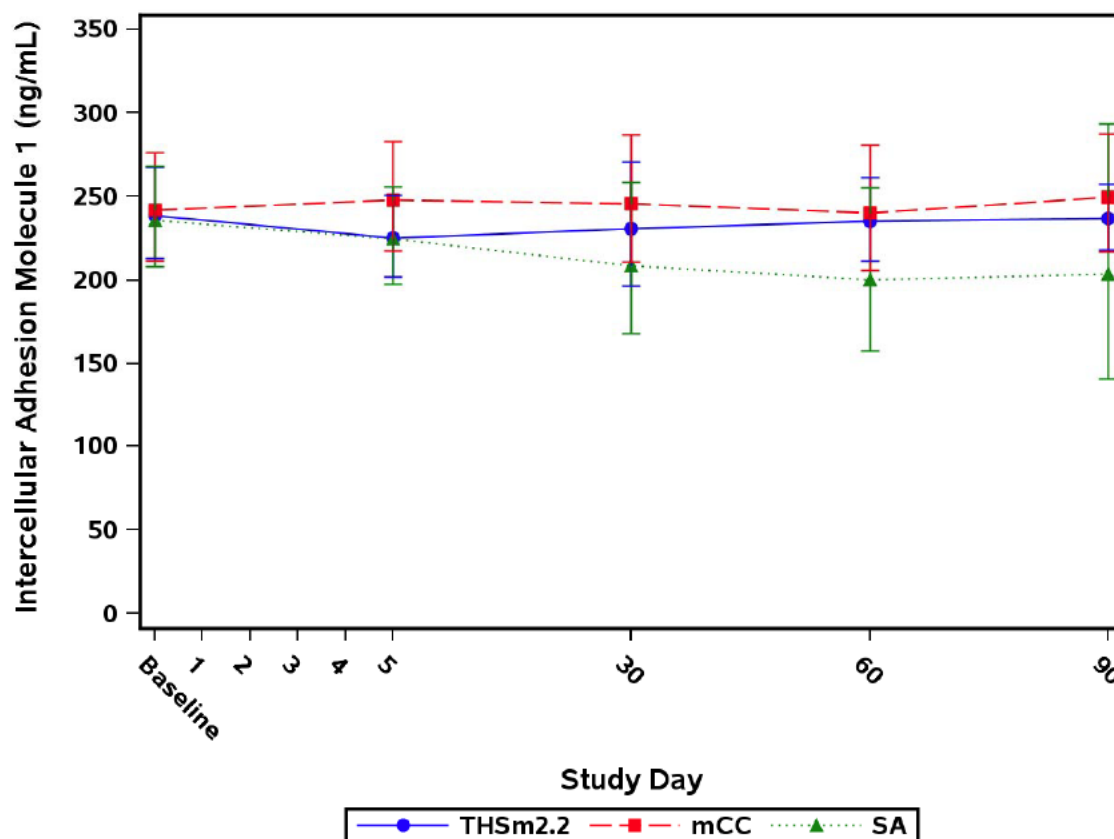
#### 11.2.6.3 Risk Marker of Endothelial Dysfunction: sICAM-1 in Serum During the Study

Subject listings of sICAM-1 data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of sICAM-1 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 percent changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#), and in [Figure 28](#).



**Figure 28 Geometric Mean and 95% CIs sICAM-1 (ng/mL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; sICAM-1 = soluble inter-cellular adhesion molecule 1; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline was defined as the last assessment prior to first 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 was summarized using the baseline data from the PP Set for Period 1.

Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.3.1.](#)

At baseline, the geometric mean levels of sICAM-1 were comparable between the study arms, with a mean of 238.8, 241.8, and 236.0 ng/mL for the THS 2.2 Menthol, mCC, and SA arms, respectively. At Discharge on Day 6, the geometric mean values of sICAM-1 had decreased in the THS 2.2 Menthol and SA arms and were comparable to baseline in the mCC arm, with median changes from baseline at Discharge of -5.0%, 0.0%, and -10.2% for the THS 2.2 Menthol, mCC, and SA arms, respectively.

During the Ambulatory Period, levels of sICAM-1 remained comparable to baseline for the THS 2.2 Menthol and mCC arms, while levels decreased in the SA arm. Median



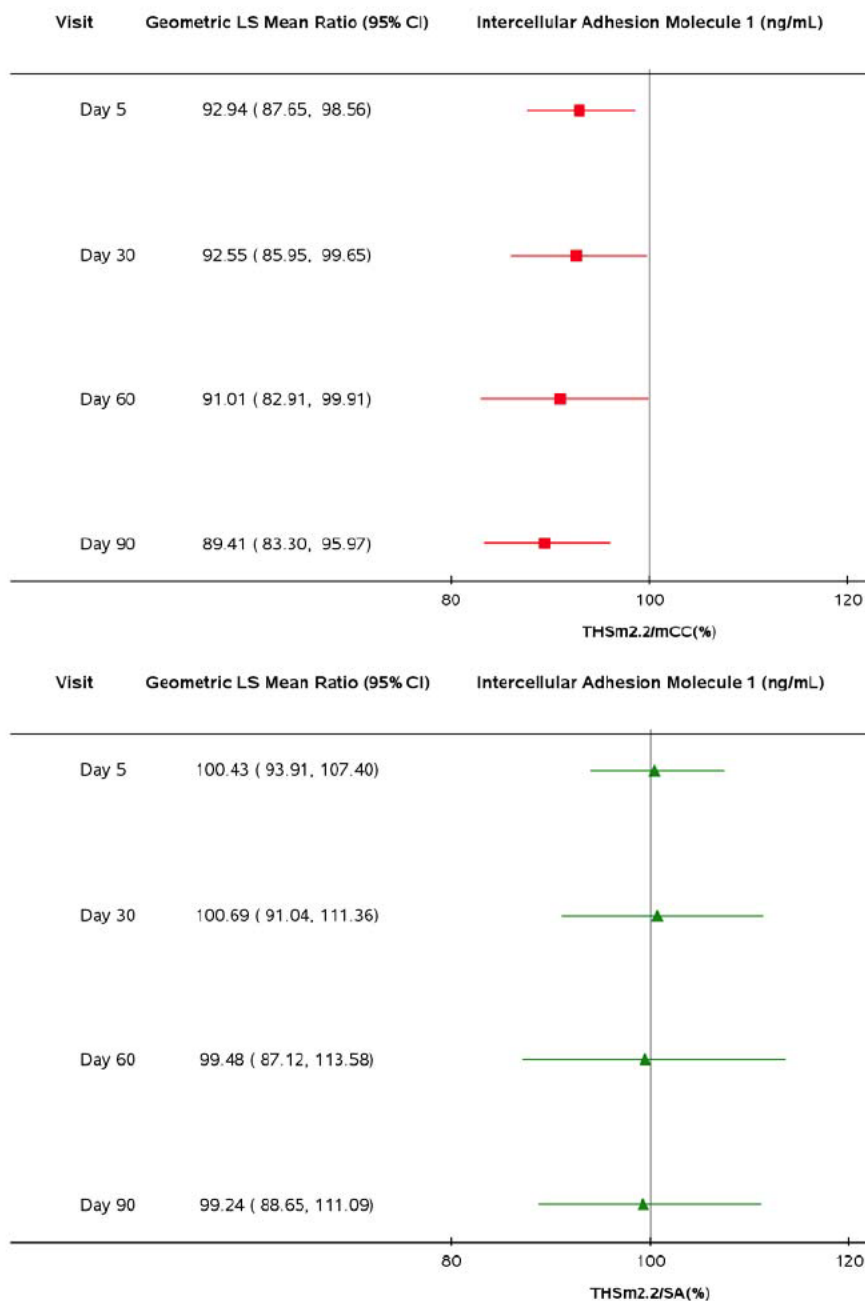


changes from baseline on Day 90 were -6.7%, 5.4%, and -8.1% for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Analyses for THS 2.2 Menthol use versus mCC use and SA on Day 91/Discharge Ambulatory 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 and are also graphically presented in [Appendix 15, Figure 15.1.2.2](#). The statistical analyses are also presented in [Figure 29](#).



**Figure 29 Forest Plot of Statistical Analysis of sICAM-1 (ng/mL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)



On Days 6, 30, 60, and 90, the LS means of sICAM-1 were 7.06%, 7.45%, 8.99%, and 10.59% lower, respectively, for subjects who switched to THS 2.2 Menthol use compared to subjects who continued smoking mCC, with all 95% CIs excluding 100%.

There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Days 5, 30, 60, and 90, with the 95% CIs spanning 100%.

The results for the FAS were consistent with the results for the PP Set.

#### 11.2.6.4 Risk Markers of Lipid Metabolism: Triglycerides, Total Cholesterol, HDL Cholesterol, LDL Cholesterol, and Apolipoprotein A1 and B in Serum During the Study

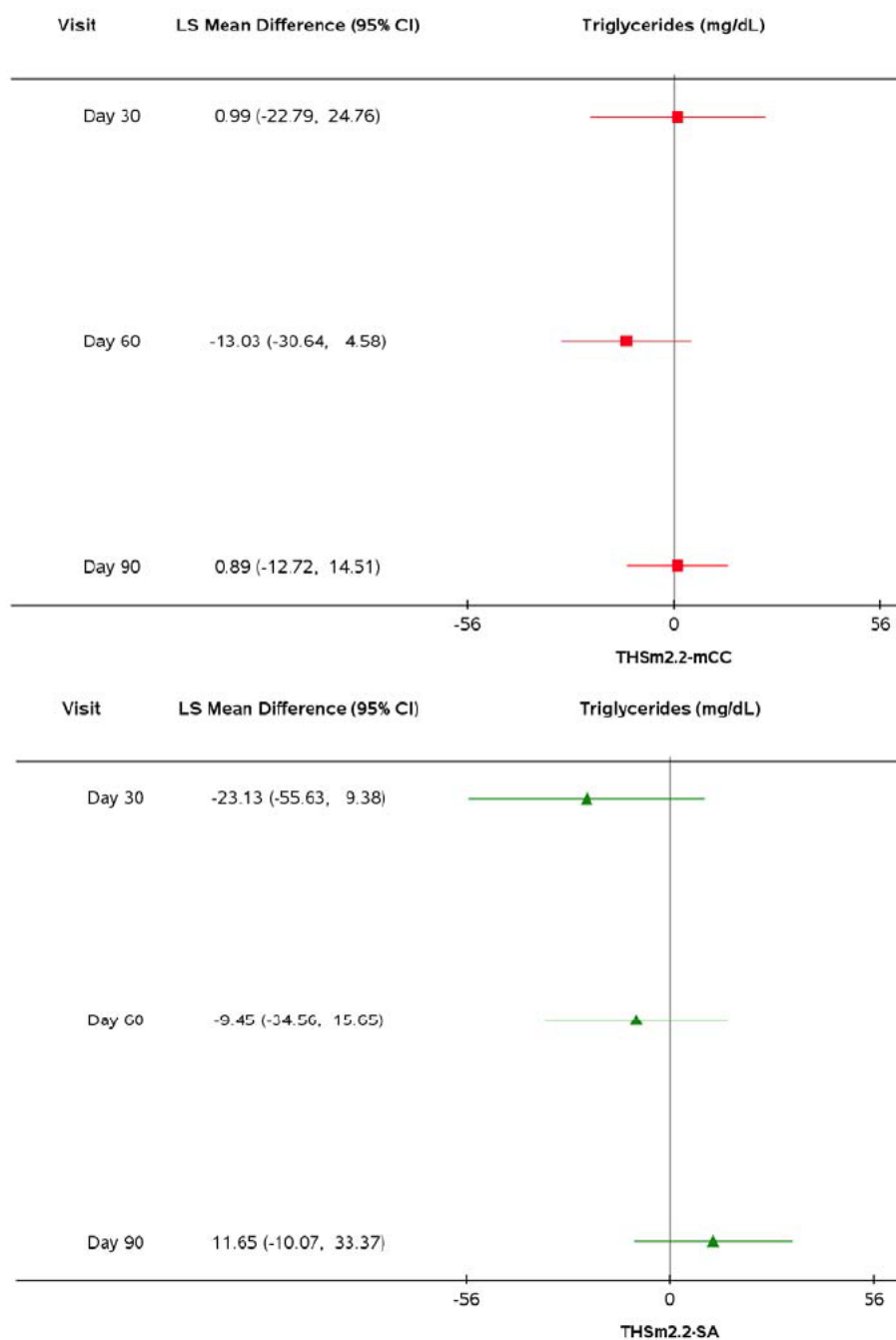
Subject listings of TG, TC, LDL-C, HDL-C, Apo A1, and Apo B in serum data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of TG, TC, LDL-C, HDL-C, Apo A1, and Apo B 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 percent 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 versus SA during the study are presented 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 TG, TC, HDL-C, LDL-C, Apo A1, and Apo B are also presented graphically in [Appendix 15, Figure 15.1.2.2](#) and in [Figure 30, Figure 31, Figure 32, Figure 33, Figure 34, and Figure 35](#) respectively.



**Figure 30 Forest Plot of Statistical Analysis of Triglycerides (mg/dL) During the Course of the Study (PP Set)**

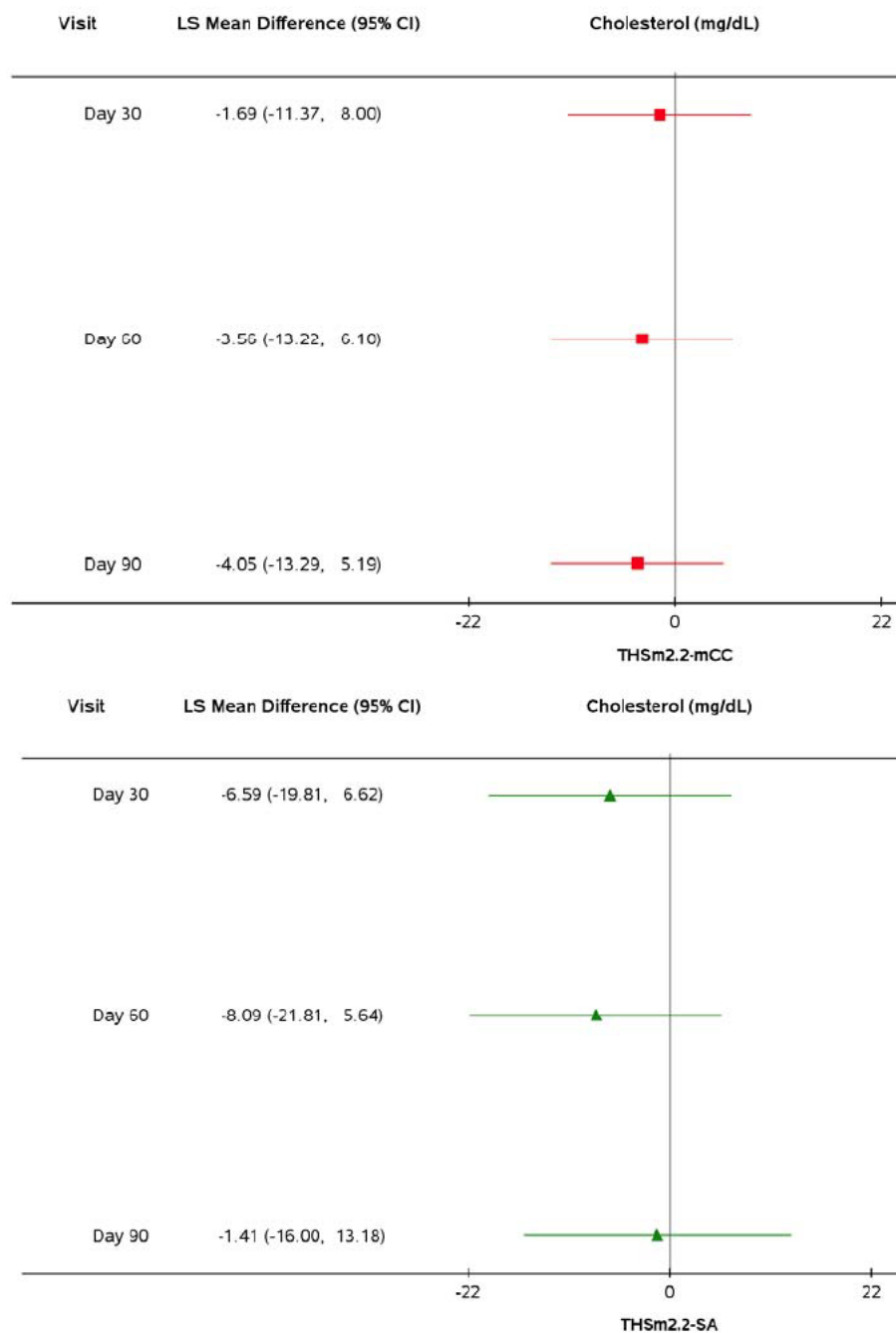


Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.  
Data Source: [Appendix 15, Figure 15.1.2.2](#)





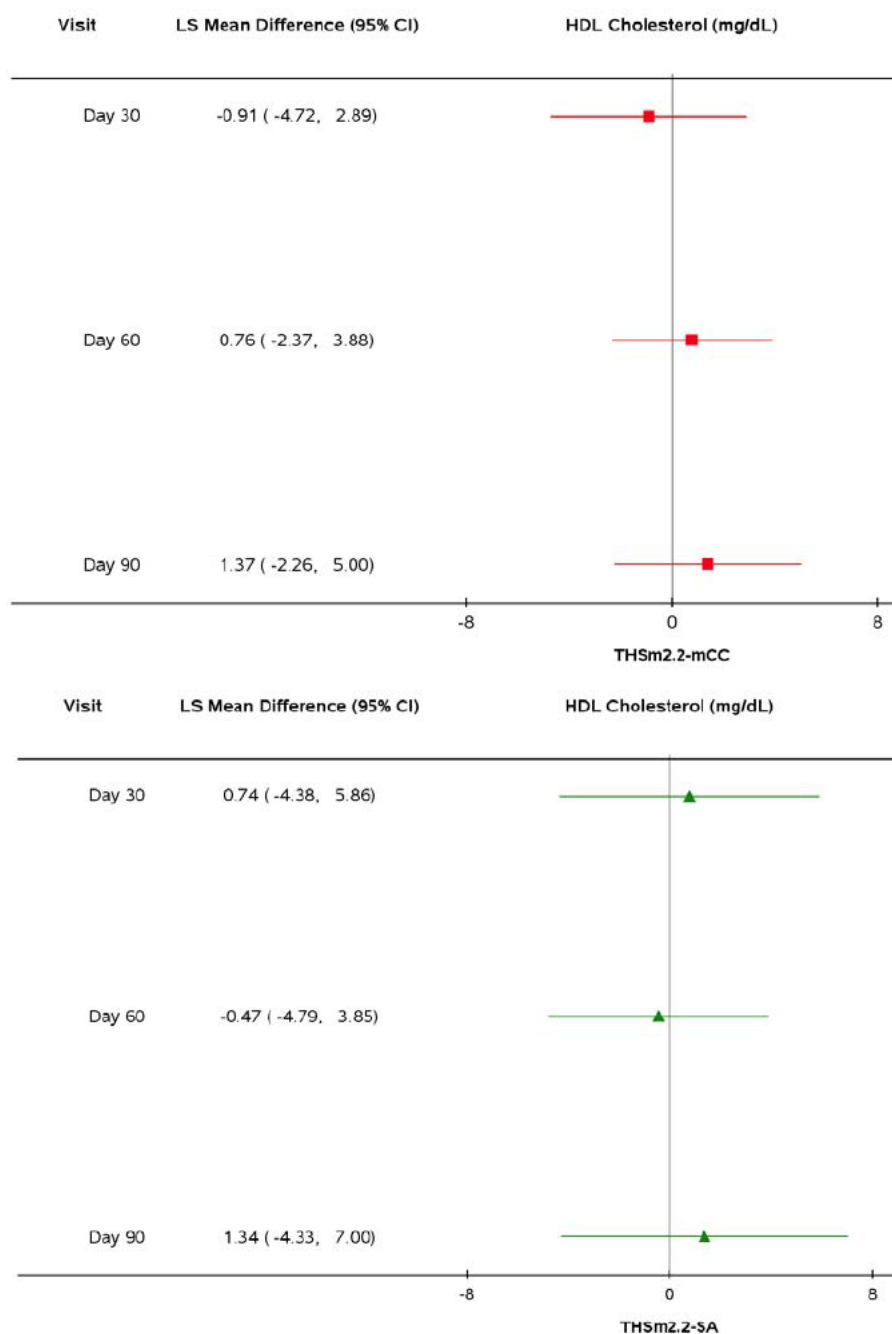
**Figure 31 Forest Plot of Statistical Analysis of Total Cholesterol (mg/dL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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](#)



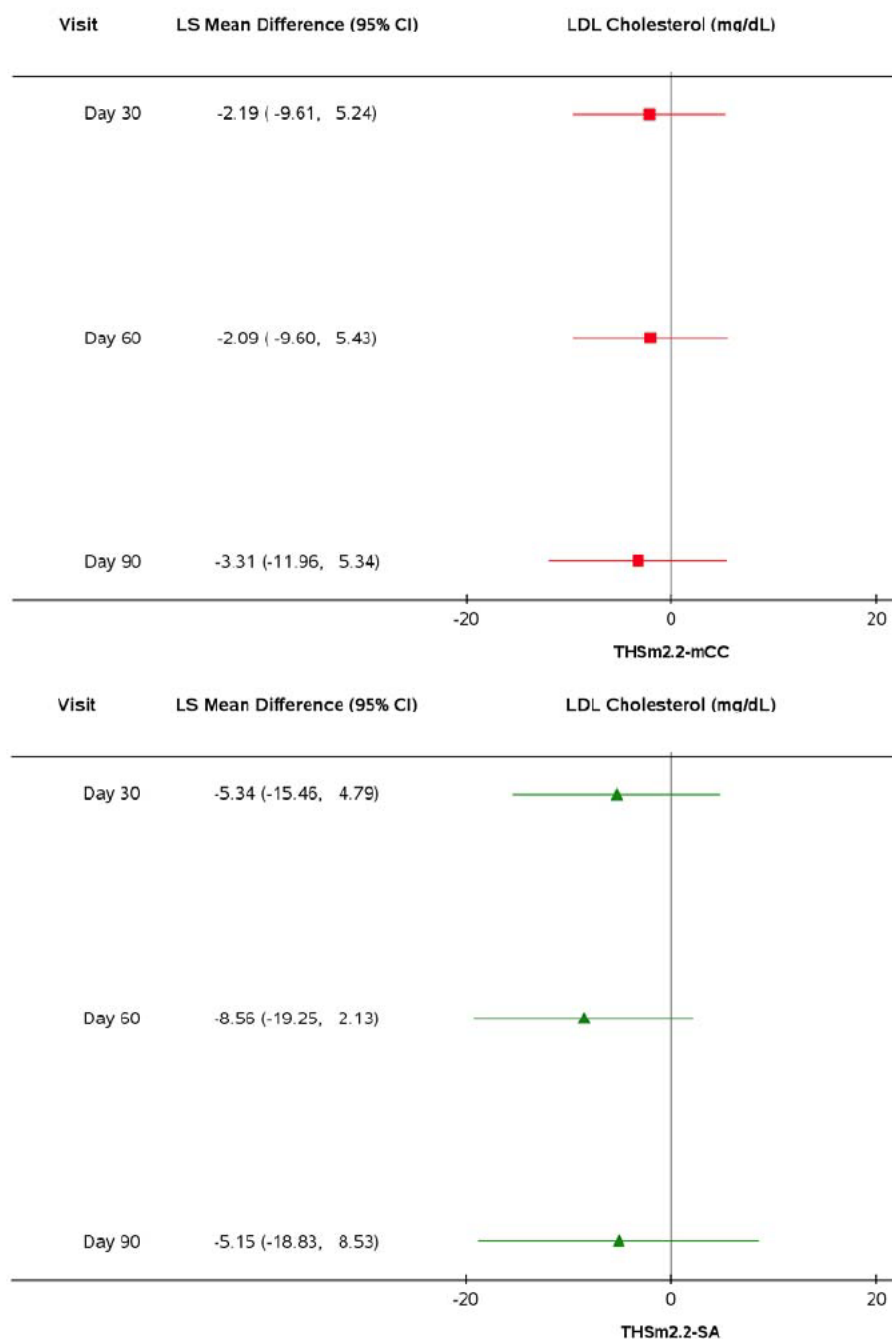
**Figure 32 Forest Plot of Statistical Analysis of HDL Cholesterol (mg/dL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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.](#)



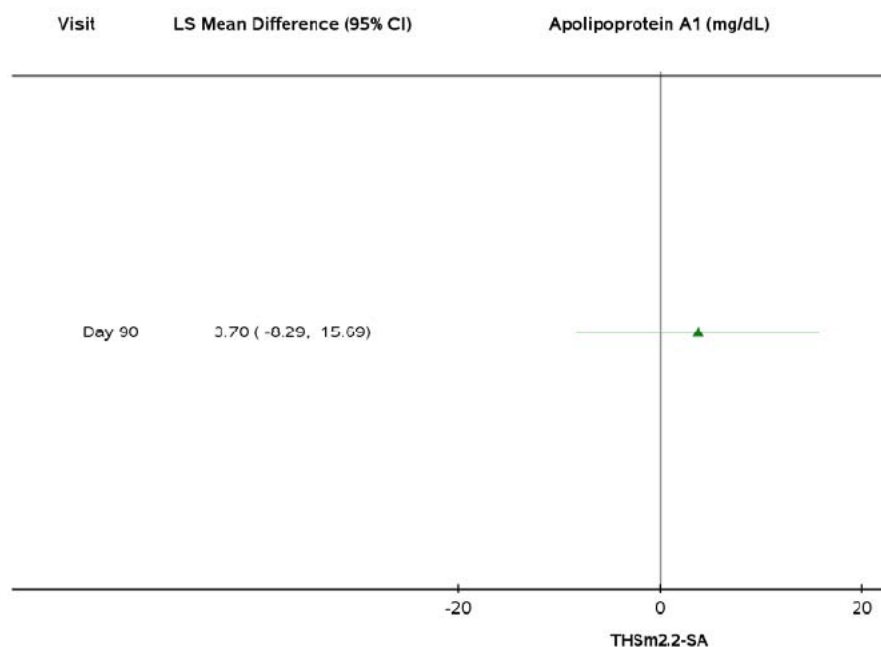
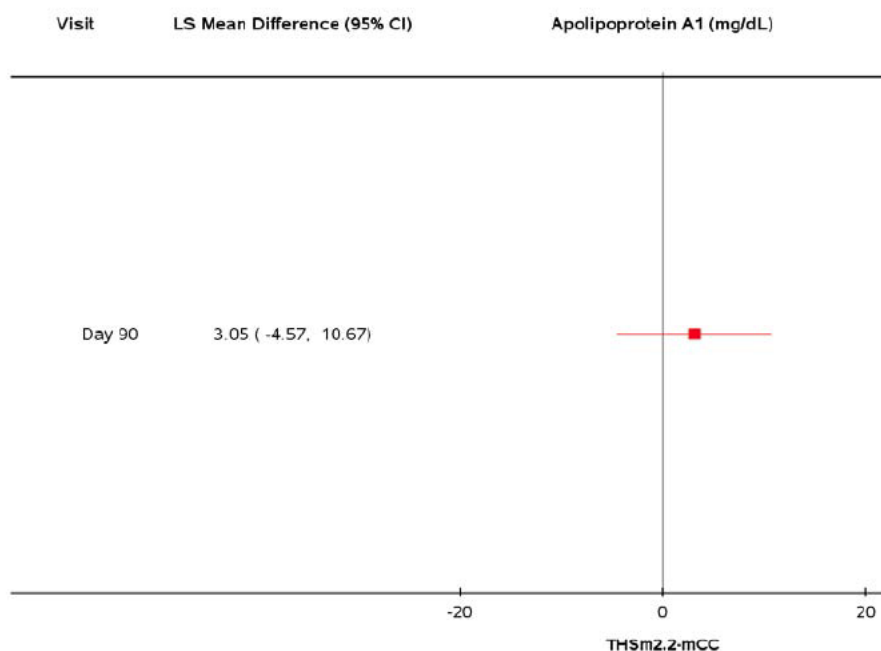
**Figure 33 Forest Plot of Statistical Analysis of LDL Cholesterol (mg/dL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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.](#)



**Figure 34 Forest Plot of Statistical Analysis of Apolipoprotein A1 (mg/dL) During the Course of the Study (PP Set)**

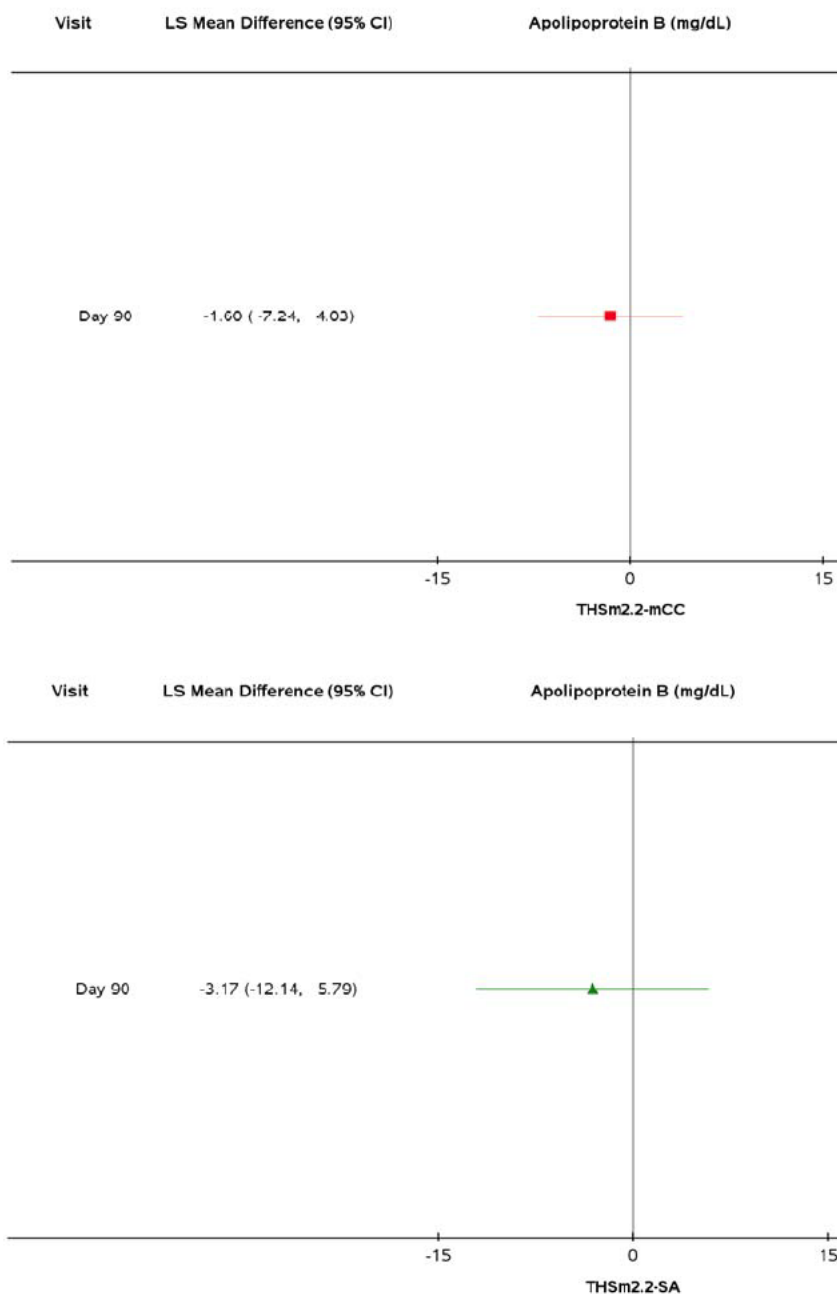


Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.  
Data Source: [Appendix 15, Figure 15.1.2.2.](#)





**Figure 35 Forest Plot of Statistical Analysis of Apolipoprotein B (mg/dL) During the Course of the Study (PP Set)**



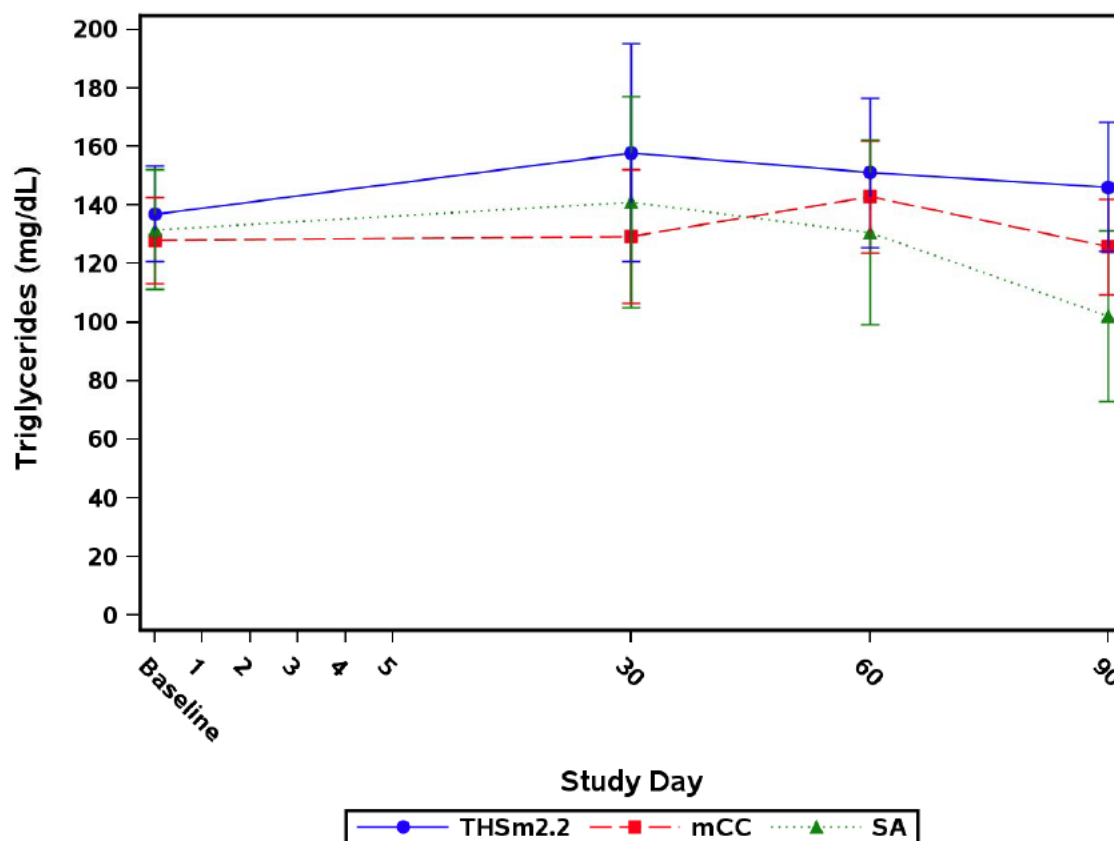
Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)



The profile of arithmetic mean triglyceride levels during the study is presented in Figure 36.

**Figure 36 Arithmetic Mean and 95% CIs Triglycerides (mg/dL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

For TG, the concentration profile for the THS 2.2 Menthol and the SA arms were similar to each other with an increase from baseline observed on Day 30 before levels fell on Days 60 and 90. In the mCC arm, triglyceride levels were similar to baseline on Day 30 before increasing on Day 60 and returning to baseline levels on Day 90. Percent changes from baseline on Day 90 of 4.4%, 4.4%, and -0.1% were observed for the THS 2.2 Menthol, mCC, and SA arms, respectively.



There were no notable differences between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at any time point in the Ambulatory Period, with the 95% CIs for the differences for all assessments spanning 0 ([Figure 31](#)).

For TC, HDL-C, and LDL-C, the mean values were comparable to baseline on Days 30, 60, and 90 for all study arms. There were no notable differences for TC, HDL-C, LDL-C, Apo A1, and Apo B between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at any time point in the Ambulatory Period, with the 95% CIs for the differences for all assessments spanning 0.

The results for the FAS were consistent with the results for the PP Set for TG and total, HDL-C, and LDL-C and Apo B, with the exception of Apo A1 which was 12.1 mg/dL higher for subjects who switched to THS 2.2 Menthol compared to subjects who abstained from smoking (95% CI: 4.9, 19.4).

#### 11.2.6.5 Risk Marker of Inflammation: Platelet Count and WBC Differential Counts in Blood During the Study

Subject listings of platelet count and WBC differential counts data are provided in [Appendix 15, Listing 15.3.6.7](#).

Descriptive statistics of platelet count and WBC 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 percent changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#).

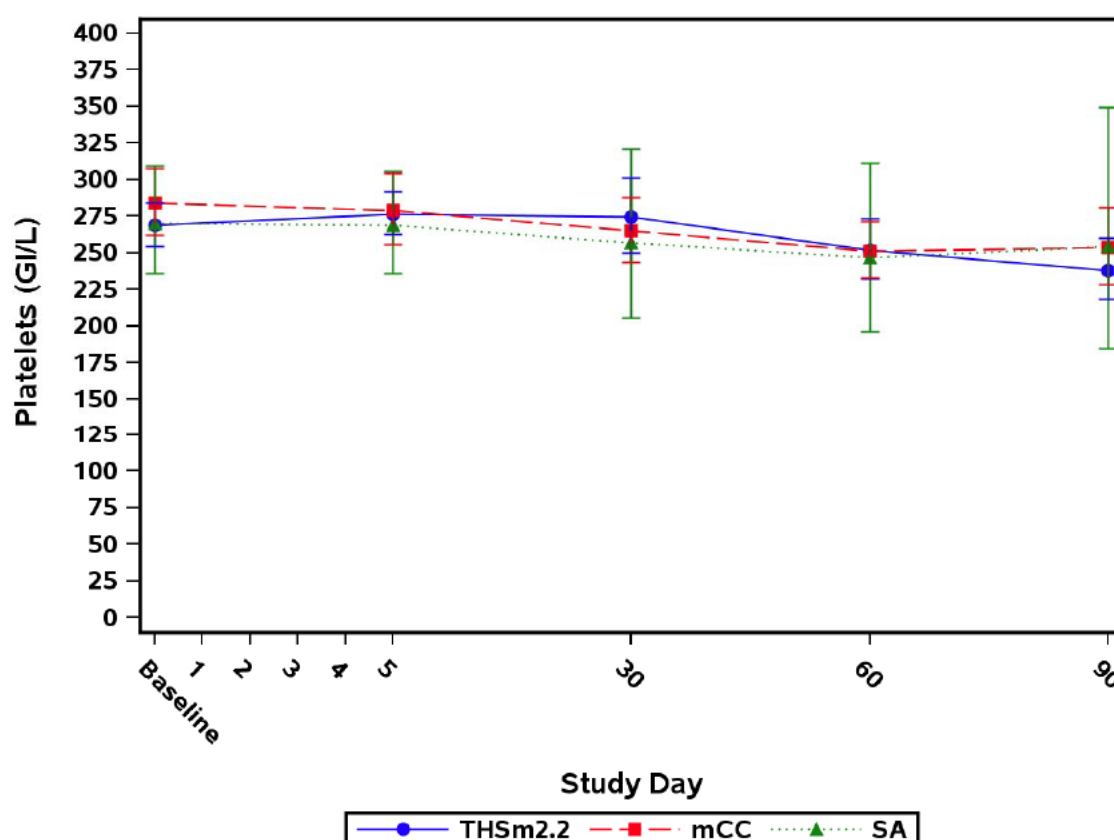
Analyses for THS 2.2 Menthol use versus mCC use and SA on Day 91/Discharge Ambulatory are tabulated in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively and are also graphically presented in [Appendix 15, Figure 15.1.2.2](#).

##### 11.2.6.5.1 Platelet Count (GI/L) During the Study

Platelet counts during the study are presented in [Figure 37](#).



**Figure 37 Geometric Mean and 95% CIs Platelets (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

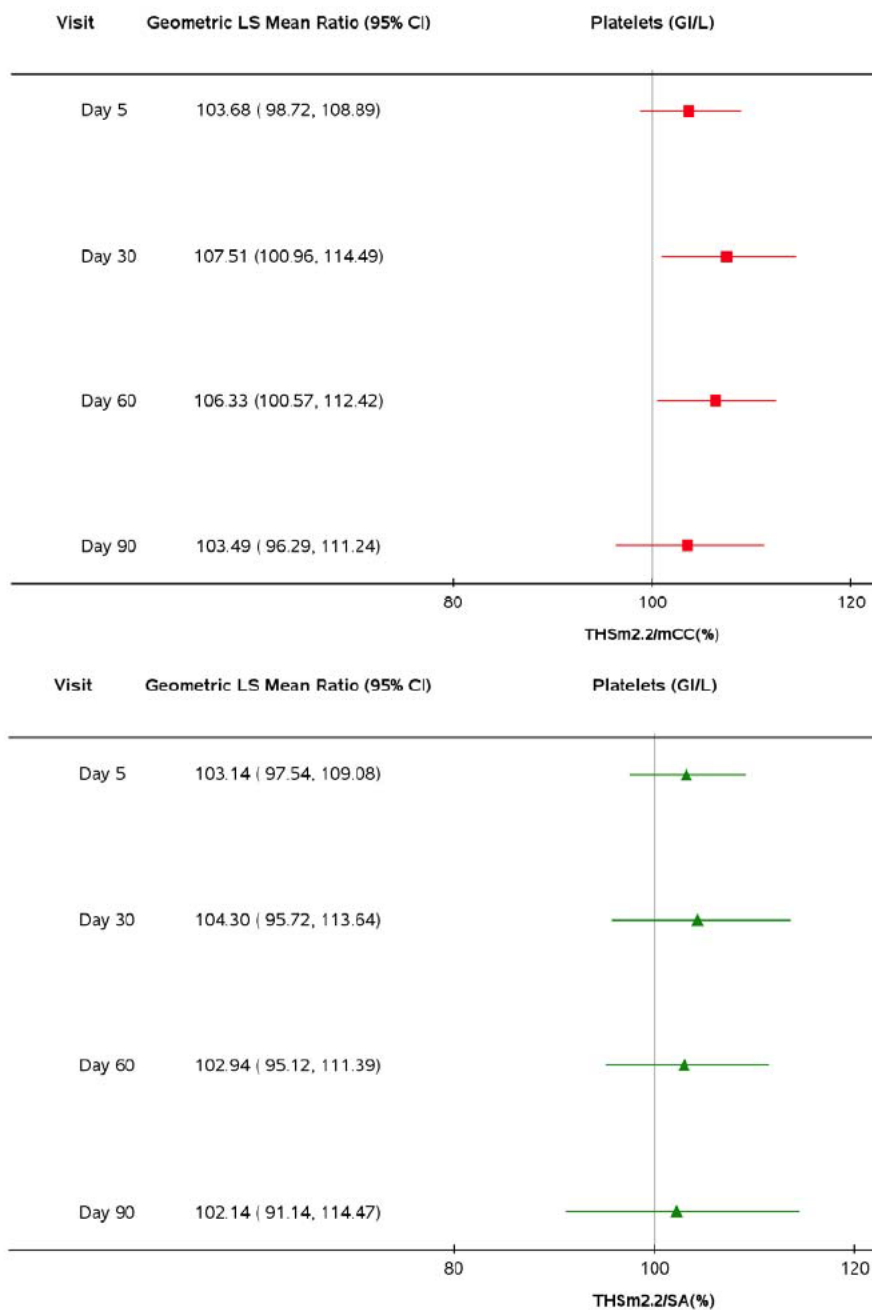
Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, platelet counts were comparable between the study arms, with a geometric mean of 268.9, 283.7, and 270.2 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively, and remained comparable throughout the Confinement Period. In the Ambulatory Period platelet count decreased modestly for all study arms and levels were comparable at the end of the Ambulatory Period, with median changes from baseline on Day 91/Discharge Ambulatory of -9.7%, -13.0%, and -7.4% for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of platelet counts on Days 6, 30, 60, and 90 are presented in [Figure 38](#).



**Figure 38 Forest Plot of Statistical Analysis of Platelets (GI/L) During the Course of the Study (PP Set)**

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.  
Data Source: [Appendix 15, Figure 15.1.2.2.](#)



On Days 30 and 60, the LS means for platelet count were 7.51% and 6.33% higher, respectively, for subjects who switched to THS 2.2 Menthol use compared to subjects who continued smoking mCC, with the 95% CIs excluding 100%. There were no notable differences on Day 6/Discharge Confinement and Day 90.

There was no notable difference in platelet count between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Days 6, 30, 60, and 90, with the 95% CIs spanning 100%.

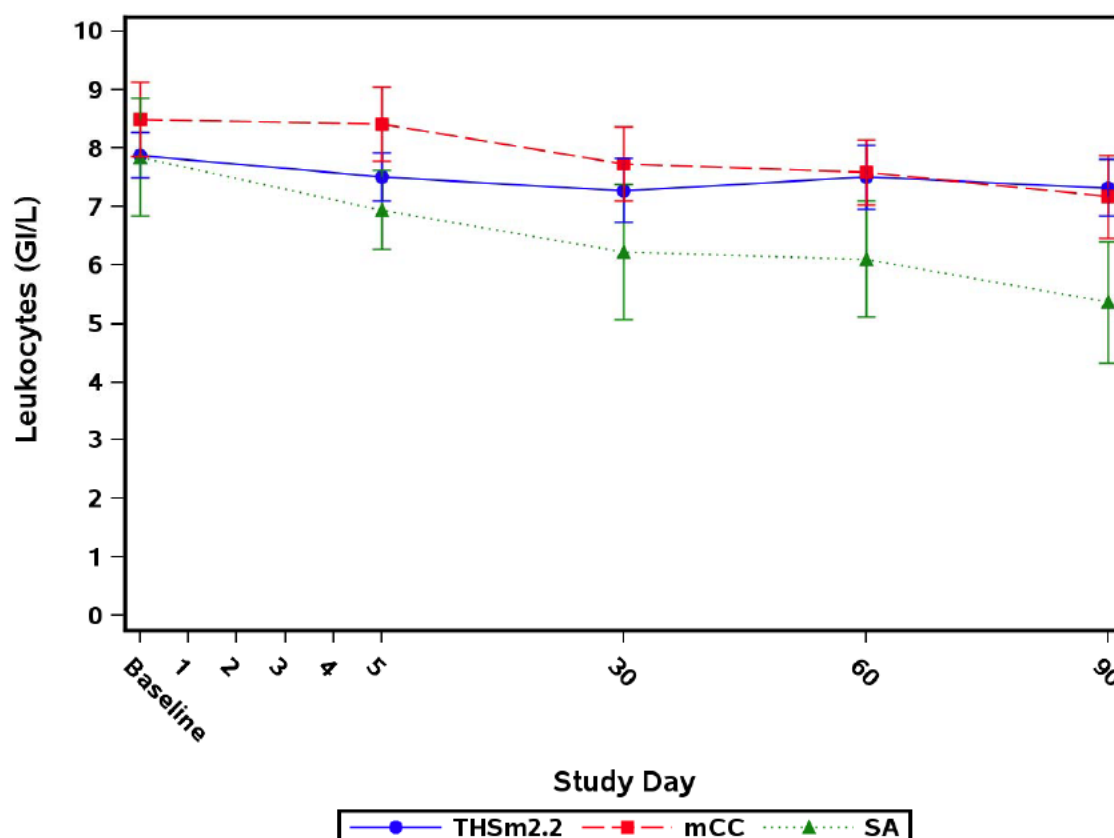
The results for the FAS were consistent with the results for the PP Set, with the exception that the 95% CI for the Day 60 comparison of THS 2.2 Menthol and mCC arms spanned 100%.

#### 11.2.6.5.2 Total White Blood Cell (Leukocytes) Count (GI/L) During the Study

White blood cell (leukocyte) levels during the study are presented in [Figure 39](#).



**Figure 39 Arithmetic Mean and 95% CIs Total WBC (Leukocytes) (GI/L) During the Course of the Study (PP Set)**



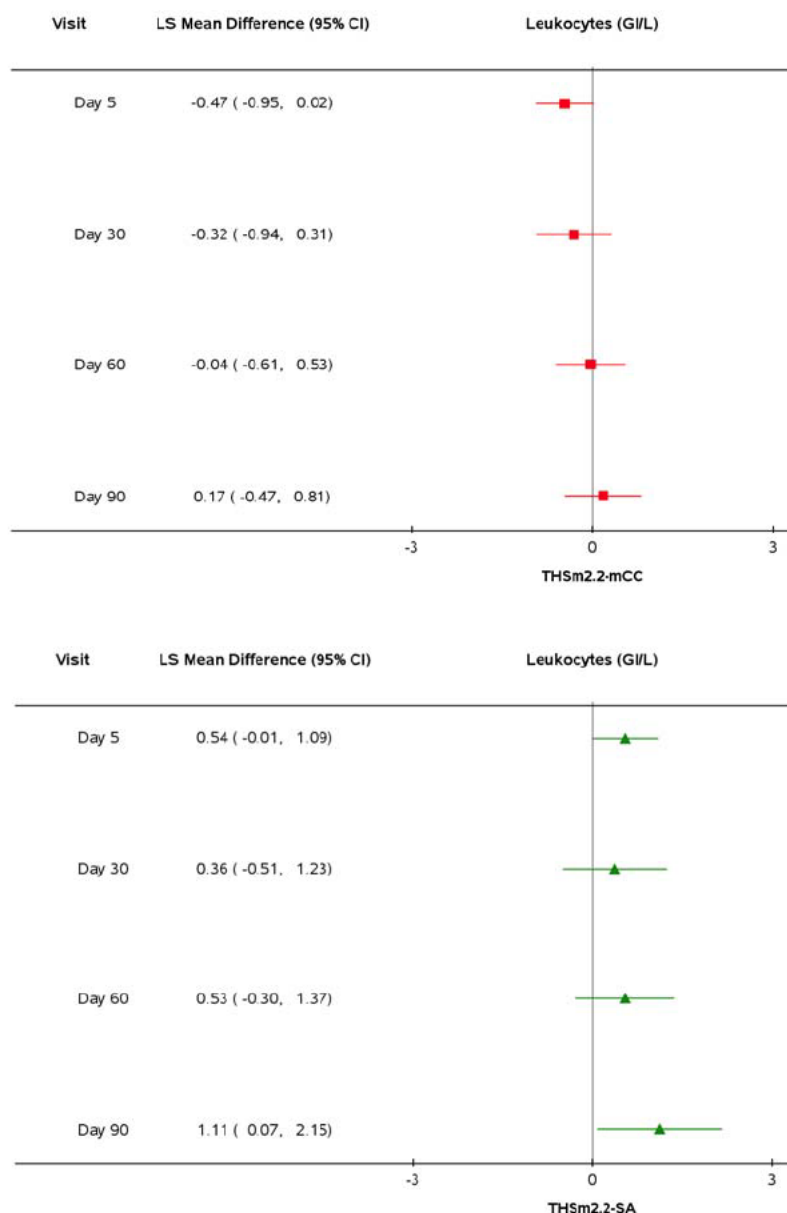
Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was defined as the last assessment prior to first product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline was summarized using the baseline data from the PP Set for Period 1. Day 5 assessment shown in the figure was carried out on Day 6. Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, total WBC (leukocyte) levels were comparable between the study arms, with a mean of 7.9, 8.5, and 7.9 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. Total WBC (leukocyte) levels decreased from baseline in the THS 2.2 Menthol and SA arms on Day 6/Discharge Confinement (change from baseline of -4.0% and -9.1%, respectively) and were stable in the mCC arm. In the Ambulatory Period total WBC (leukocyte) levels decreased modestly in the THS 2.2 Menthol and mCC arms and decreased to a greater extent in the SA arm, with changes from baseline on Day 91/Discharge Ambulatory of -10.4%, -12.5%, and -19.3% for the THS 2.2 Menthol, mCC, and SA arms, respectively.



Results of the statistical analysis of total WBC (leukocyte) levels on Days 6, 30, 60, and 90 are presented in [Figure 40](#).

**Figure 40 Forest Plot of Statistical Analysis of Total WBC (Leukocytes) (G/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.2](#).





On Day 6/Discharge Confinement, the LS mean total WBC (leukocyte) levels was 0.47 GI/L lower for subjects who switched to THS 2.2 Menthol use compared to subjects who continued smoking mCC, although the 95% CIs included 0. There were no notable differences on Days 30, 60, and 90.

There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Days 6, 30, and 60, with the 95% CIs spanning 0. The LS mean total WBC (leukocyte) level was notably higher by 1.11 GI/L on Day 90 for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.07, 2.15).

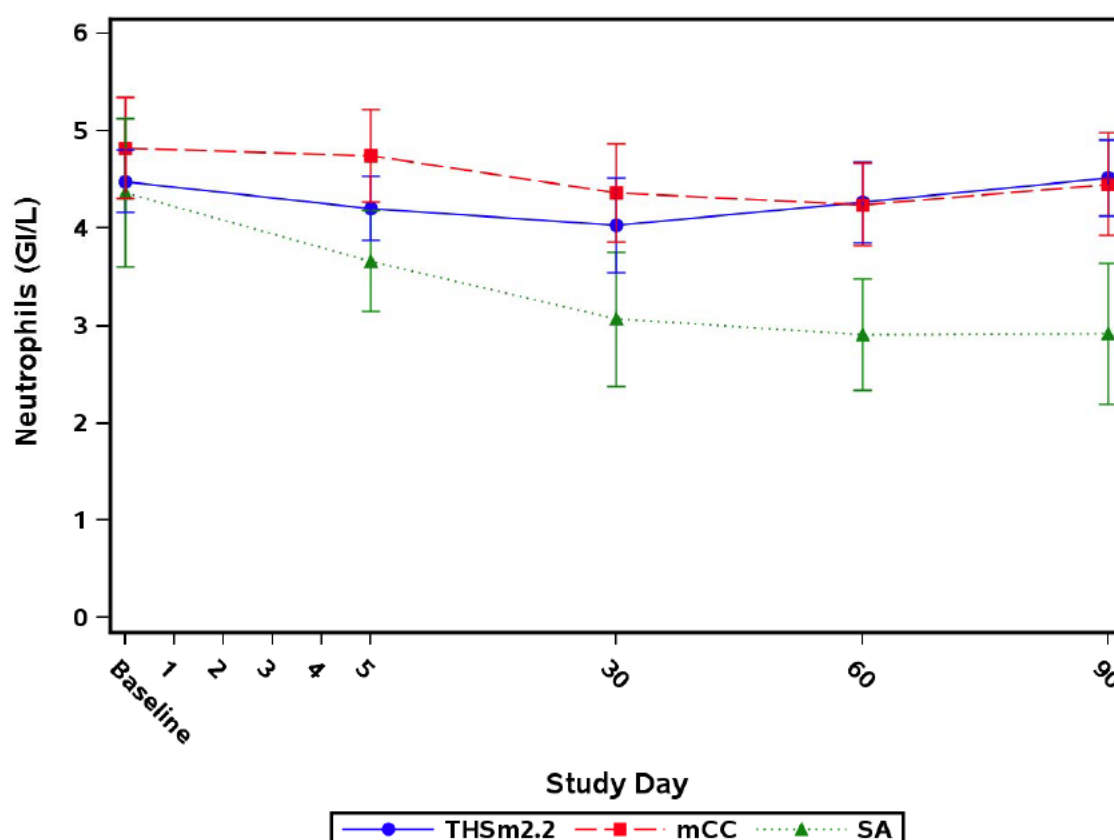
The results for the FAS were consistent with the results for the PP Set for the comparison of THS 2.2 Menthol versus mCC use. For the comparison of THS 2.2 Menthol versus SA, there were no notable differences in total WBC (leukocyte) levels at all assessment time points.

#### 11.2.6.5.3 Neutrophil Count (GI/L) During the Study

Neutrophil levels during the study are presented in [Figure 41](#).



**Figure 41 Arithmetic Mean and 95% CIs Neutrophils (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Day 5 assessment shown in the figure was carried out on Day 6.

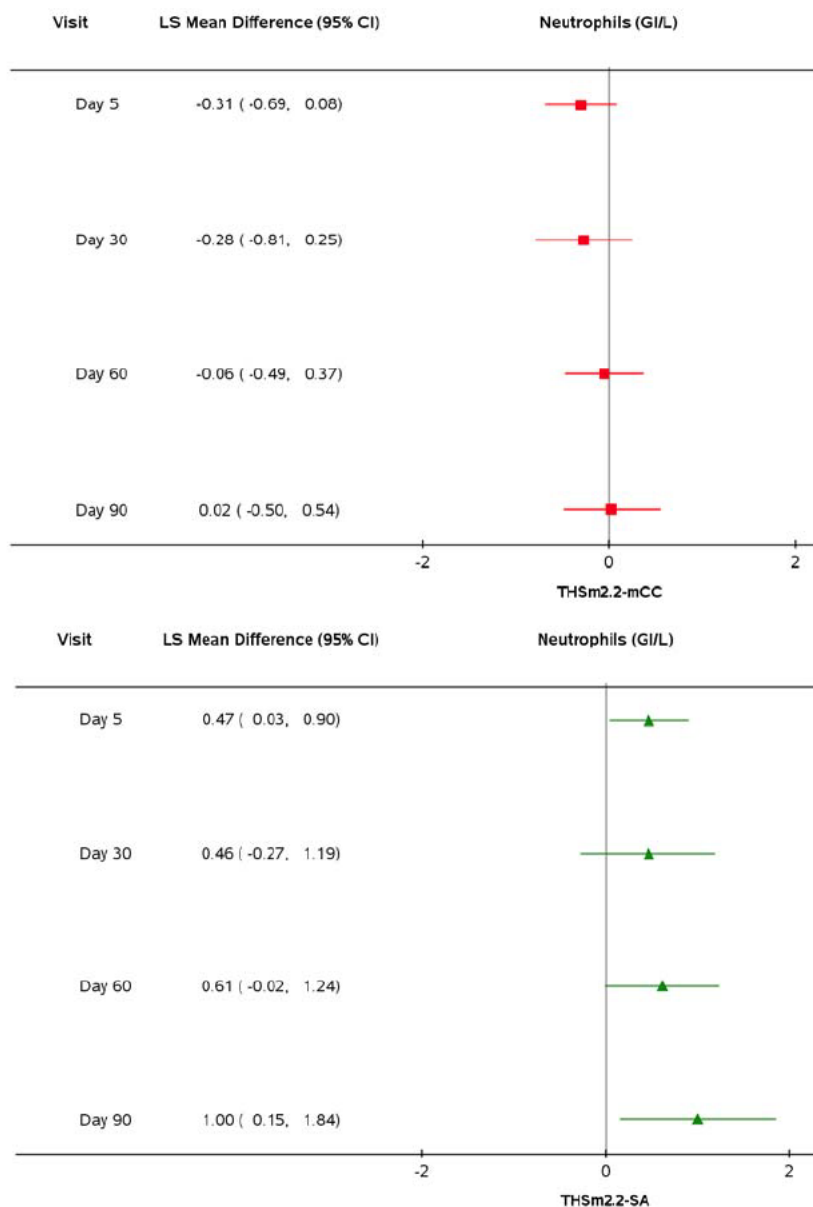
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, neutrophil levels were comparable between the study arms, with a mean of 4.5, 4.8, and 4.4 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively. Neutrophil levels decreased from baseline in the THS 2.2 Menthol and SA arms on Day 6/Discharge Confinement (changes from baseline of -4.8% and -12.5%, respectively), and was stable in the mCC arm. In the Ambulatory Period, neutrophil levels decreased modestly in the THS 2.2 Menthol and mCC arms on Day 30 before increasing to approximate baseline values on Day 90. Neutrophil levels decreased to a greater extent in the SA arm on Day 30 before plateauing thereafter. Changes from baseline on Day 91/Discharge Ambulatory were -1.8%, -1.0%, and -14.2% for the THS 2.2 Menthol,



mCC, and SA arms, respectively. Results of the statistical analysis of neutrophil levels on Days 6, 30, 60, and 90 are presented in [Figure 42](#).

**Figure 42 Forest Plot of Statistical Analysis of Neutrophils (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.  
Data Source: [Appendix 15, Figure 15.1.2.2](#).



There was no notable difference in LS mean neutrophil levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

The LS mean neutrophil level was notably higher by 0.47, 0.46, 0.61, and 1.00 GI/L on Days 6, 30, 60, and 90, respectively, for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking although the 95% CIs only excluded 0 on Day 6/Discharge Confinement and Day 90.

The results for the FAS were consistent with the results for the PP Set for the comparison of THS 2.2 Menthol versus mCC use. For the comparison of THS 2.2 Menthol versus SA, there were no notable differences in neutrophil levels between subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking on Days 6, 30, 60, and 90.

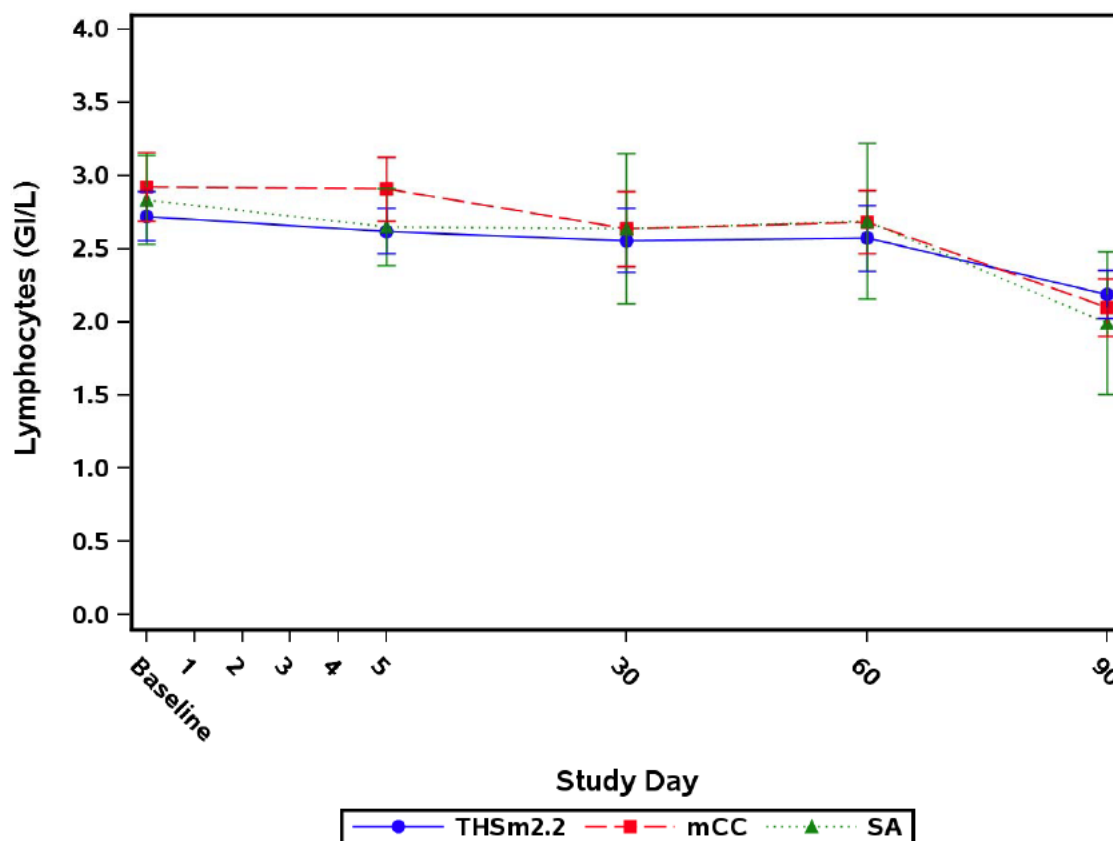
#### 11.2.6.5.4 Lymphocyte Count (GI/L) During the Study

Lymphocyte levels during the study are presented in [Figure 43](#).





**Figure 43 Arithmetic Mean and 95% CIs Lymphocytes (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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.

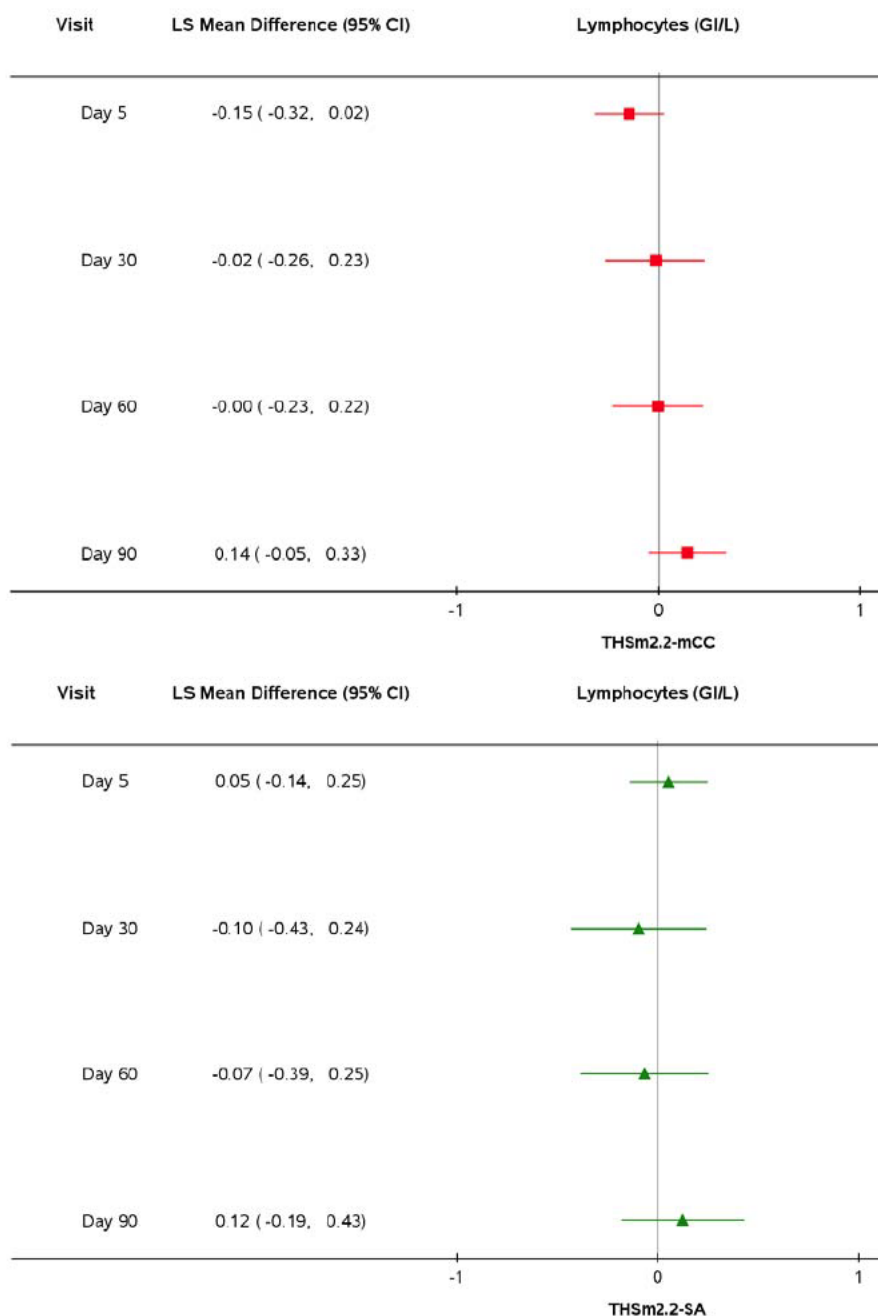
Baseline was summarized using the baseline data from the PP Set for Period 1.

Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, lymphocyte levels were comparable between the study arms, with a mean of 2.7, 2.9, and 2.8 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively, and remained stable for the remainder of the study. On Day 90, mean lymphocyte levels were 2.2, 2.1, and 2.0 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of lymphocyte levels on Days 6, 30, 60, and 90 are presented in [Figure 44](#).

**Figure 44 Forest Plot of Statistical Analysis of Lymphocytes (GI/L) During the Course of the Study (PP Set)**

Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.  
Data Source: [Appendix 15, Figure 15.1.2.2.](#)



There was no notable difference in LS mean lymphocyte levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

There was no notable difference in lymphocyte levels between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

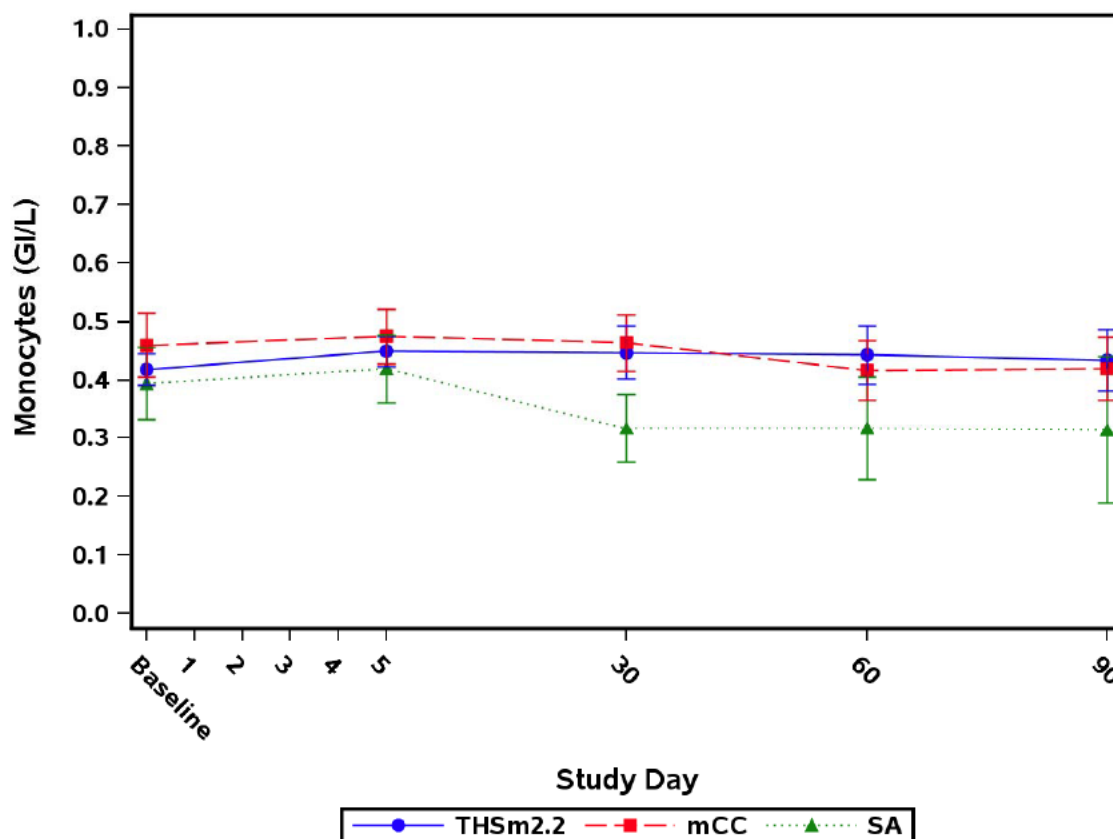
The results for the FAS were consistent with the results for the PP Set.

#### 11.2.6.5.5 Monocyte Count (GI/L) During the Study

Monocyte levels during the study are presented in [Figure 45](#).



**Figure 45 Arithmetic Mean and 95% CIs Monocytes (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

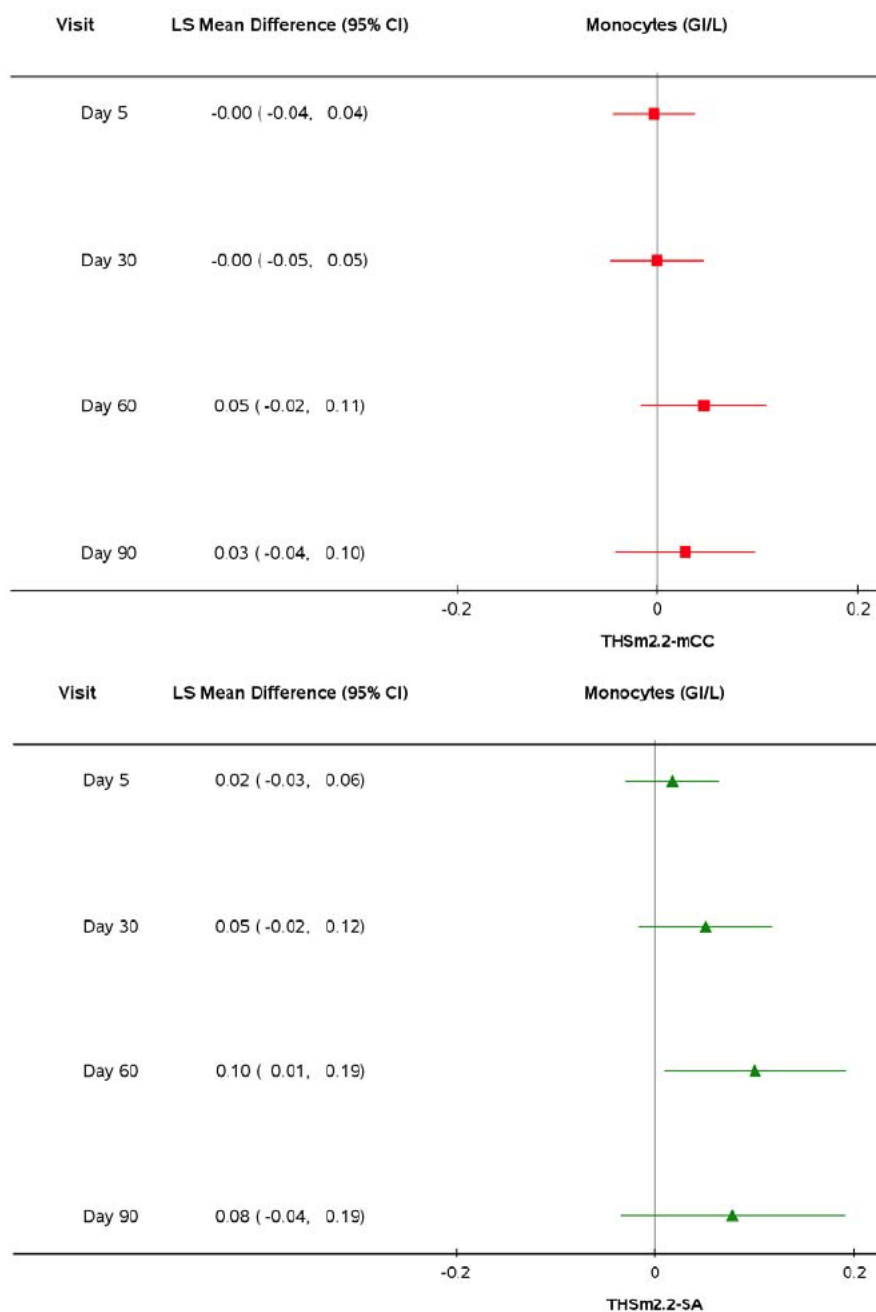
At baseline, monocyte levels were comparable between the study arms, with a mean of 0.4, 0.5, and 0.4 GI/L for the THS 2.2 Menthol, mCC, and SA arms, respectively, and remained stable for the remainder of the study for the THS 2.2 Menthol and mCC arms. In the SA arm, monocyte levels were stable for the Confinement Period but decreased from Day 6/Discharge Confinement to Day 30 before stabilizing for the remainder of the Ambulatory Period. On Day 90, mean monocyte levels were 0.4 GI/L for the THS 2.2 Menthol and mCC arms, and 0.3 GI/L for the SA arm (change from baseline of -5.4%).

Results of the statistical analysis of monocyte levels on Days 6, 30, 60, and 90 are presented in [Figure 46](#).





**Figure 46 Forest Plot of Statistical Analysis of Monocytes (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.  
Data Source: [Appendix 15, Figure 15.1.2.2.](#)



There was no notable difference in LS mean monocyte levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

The LS mean monocyte level was notably higher by 0.10 GI/L on Day 60 for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking with the 95% CIs excluding 0. There were no notable differences on Days 6, 30, and 90.

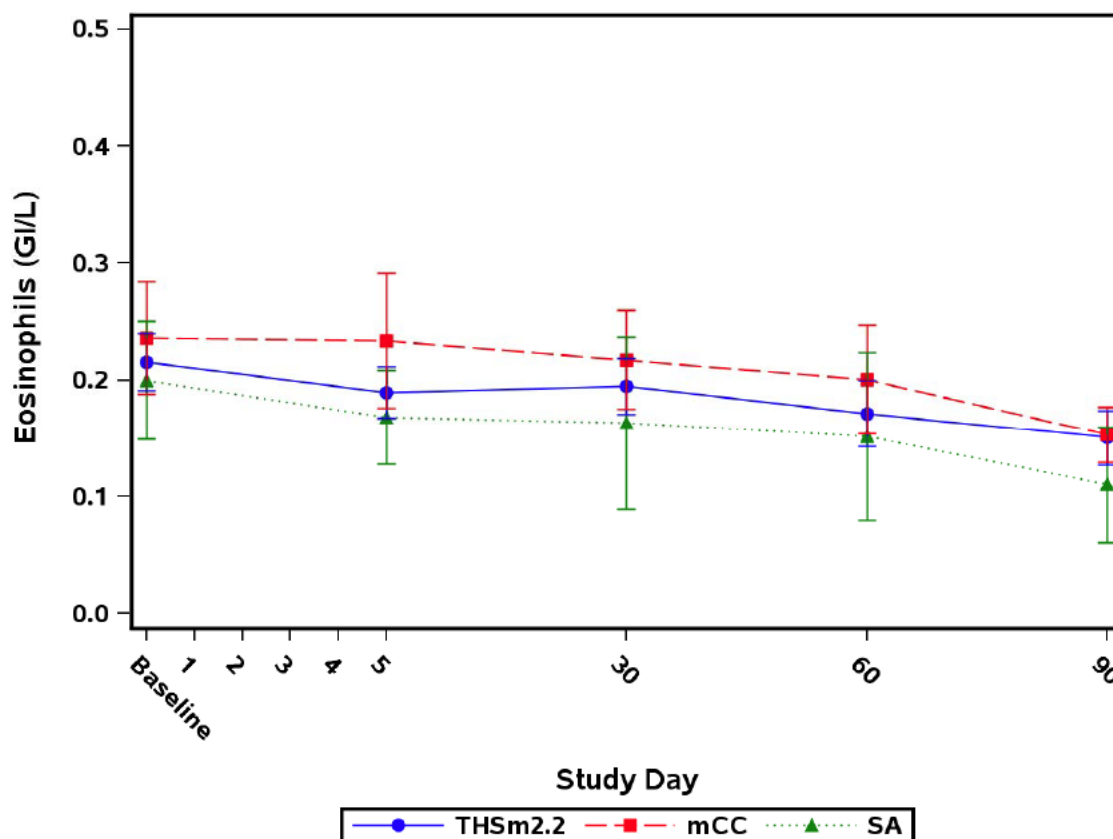
The results for the FAS were consistent with the results for the PP Set, for the comparison of THS 2.2 Menthol versus mCC use. For the comparison of THS 2.2 Menthol versus SA, there were no notable differences in monocyte levels between subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking on Days 6, 30, 60, and 90.

#### 11.2.6.5.6 Eosinophil Count (GI/L) During the Study

Eosinophil levels during the study are presented in [Figure 47](#).



**Figure 47 Arithmetic Mean and 95% CIs Eosinophils (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Day 5 assessment shown in the figure was carried out on Day 6.

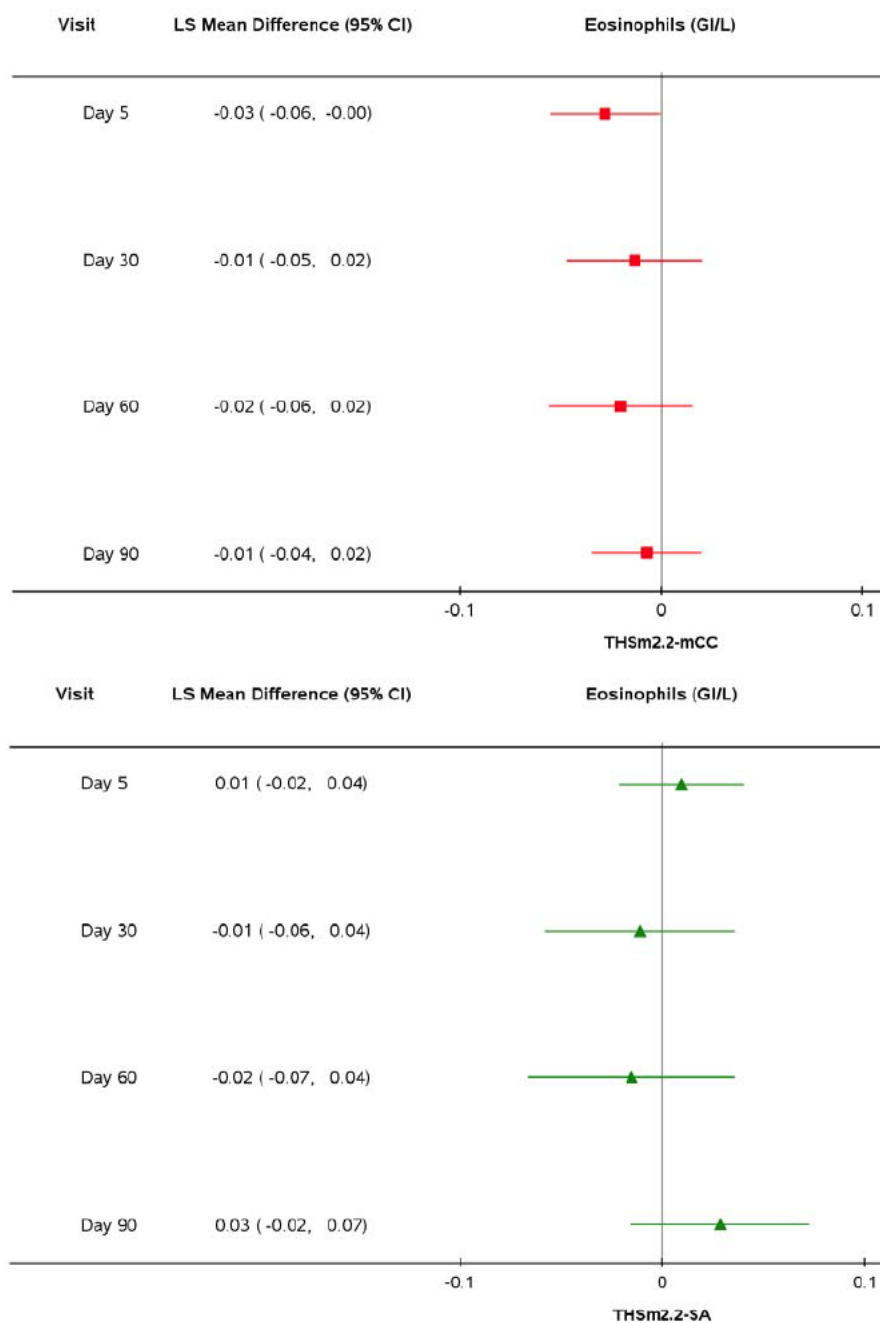
Data Source: [Appendix 15, Figure 15.1.2.3.1](#).

At baseline, eosinophil levels were identical between the study arms, with a mean of 0.2 GI/L and remained stable through the Confinement Period and Day 30 before decreasing in the remainder of the Ambulatory Period for all study arms. Changes from baseline on Day 90 were -27.0%, -22.0%, and -39.0% for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of eosinophil levels on Days 6, 30, 60, and 90 are presented in [Figure 48](#).



**Figure 48 Forest Plot of Statistical Analysis of Eosinophils (G/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.  
Data Source: [Appendix 15, Figure 15.1.2.2.](#)





There was no notable difference in LS mean eosinophil levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

There was no notable difference in LS mean eosinophil levels between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

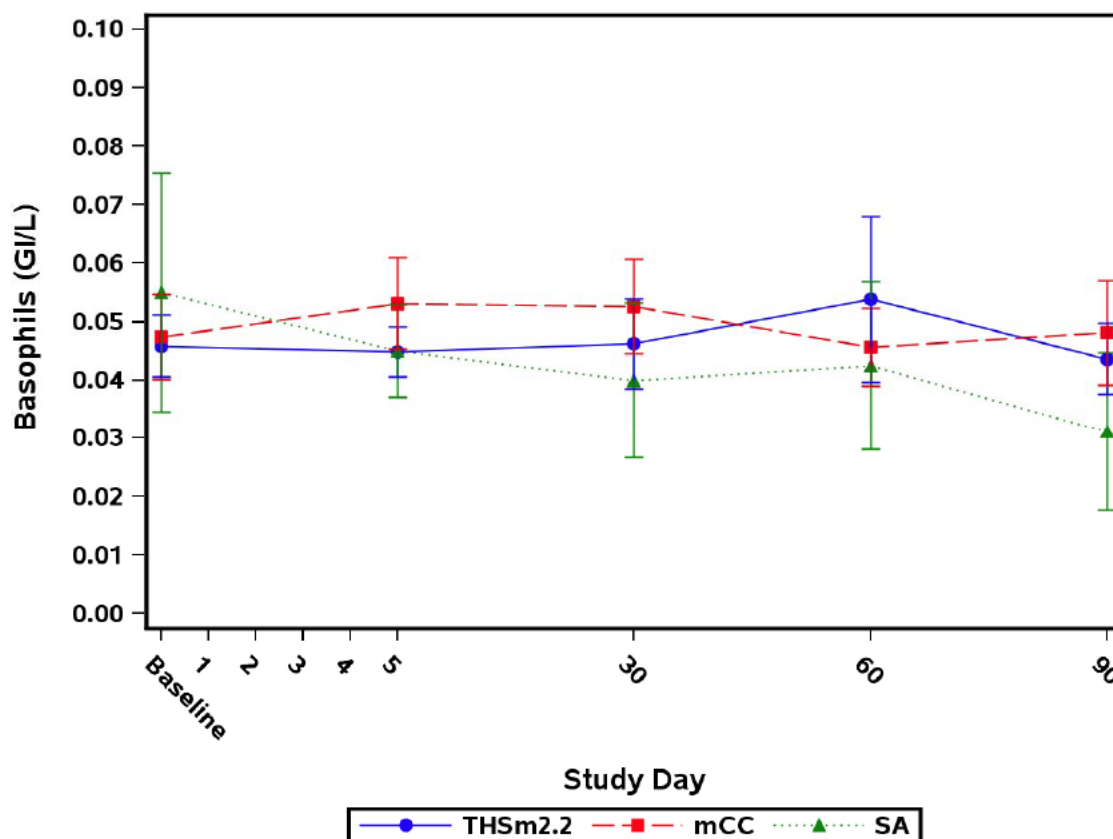
The results for the FAS were consistent with the results for the PP Set.

#### 11.2.6.5.7 Basophil Count (GI/L) During the Study

Basophil levels during the study are presented in [Figure 49](#).



**Figure 49 Arithmetic Mean and 95% CIs Basophils (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Day 5 assessment shown in the figure was carried out on Day 6.

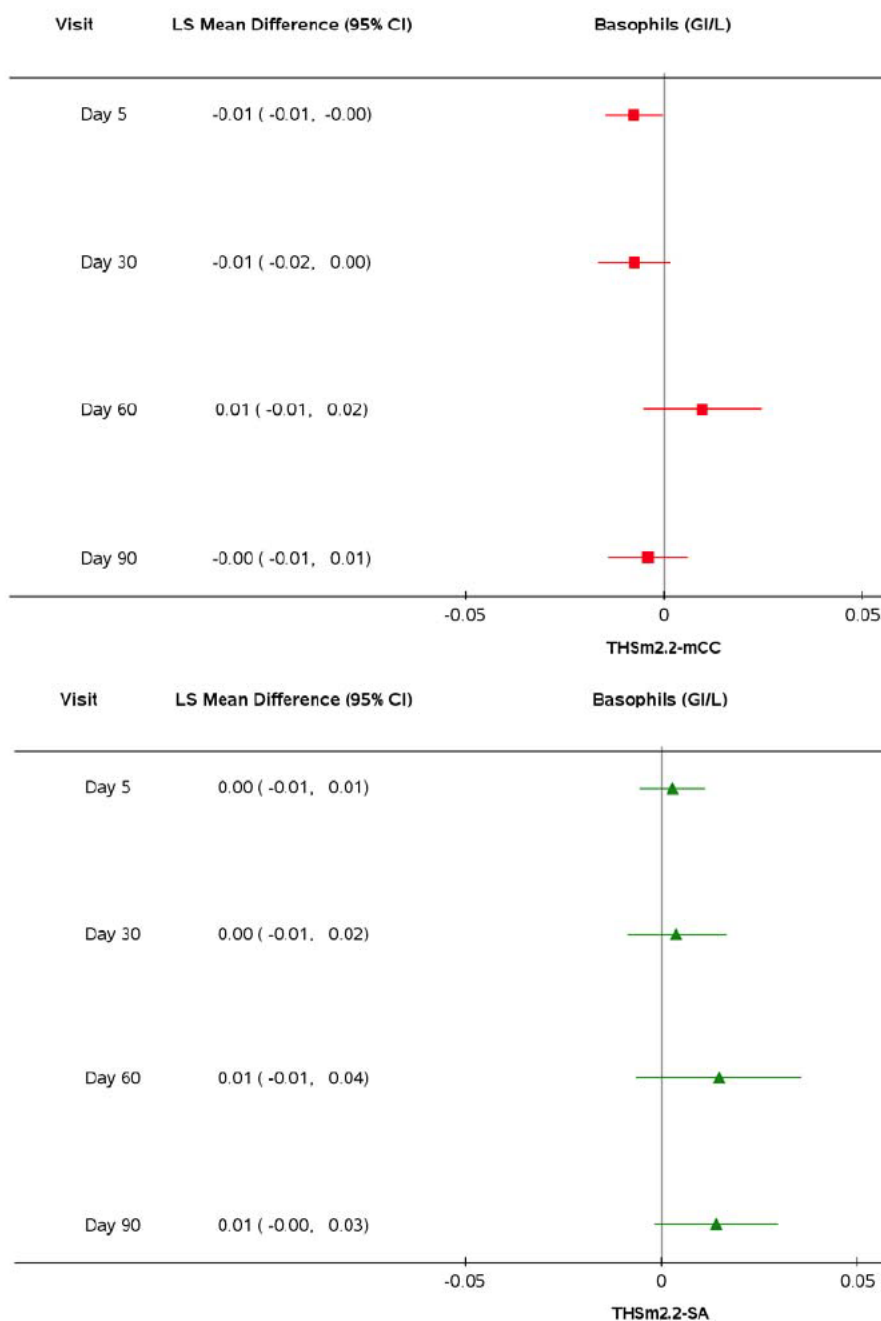
Data Source: [Appendix 15, Figure 15.1.2.3.1.](#)

At baseline, basophil levels were comparable between the study arms, and remained comparable to baseline throughout the Confinement and Ambulatory Periods for the THS 2.2 Menthol and mCC arms. In the SA arm, basophil levels slowly decreased over the course of the study. Changes from baseline on Day 90 were -2.6%, 22.1% (median change from baseline 0.0%), and -10.9% for the THS 2.2 Menthol, mCC, and SA arms, respectively.

Results of the statistical analysis of basophil levels on Days 6, 30, 60, and 90 are presented in [Figure 50](#).



**Figure 50 Forest Plot of Statistical Analysis of Basophils (GI/L) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)



There was no notable difference in LS mean basophil levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

There was no notable difference in LS mean basophil levels between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking on Days 6, 30, 60, and 90, with the 95% CIs spanning 0.

The results for the FAS were consistent with the results for the PP Set.

#### 11.2.6.6 Risk Markers for Cardiovascular Risk Monitoring: Homocysteine, Fibrinogen, and hs-CRP During the Study

Subject listings of homocysteine, fibrinogen, and hs-CRP data are provided in [Appendix 15, Listing 15.3.3.2](#).

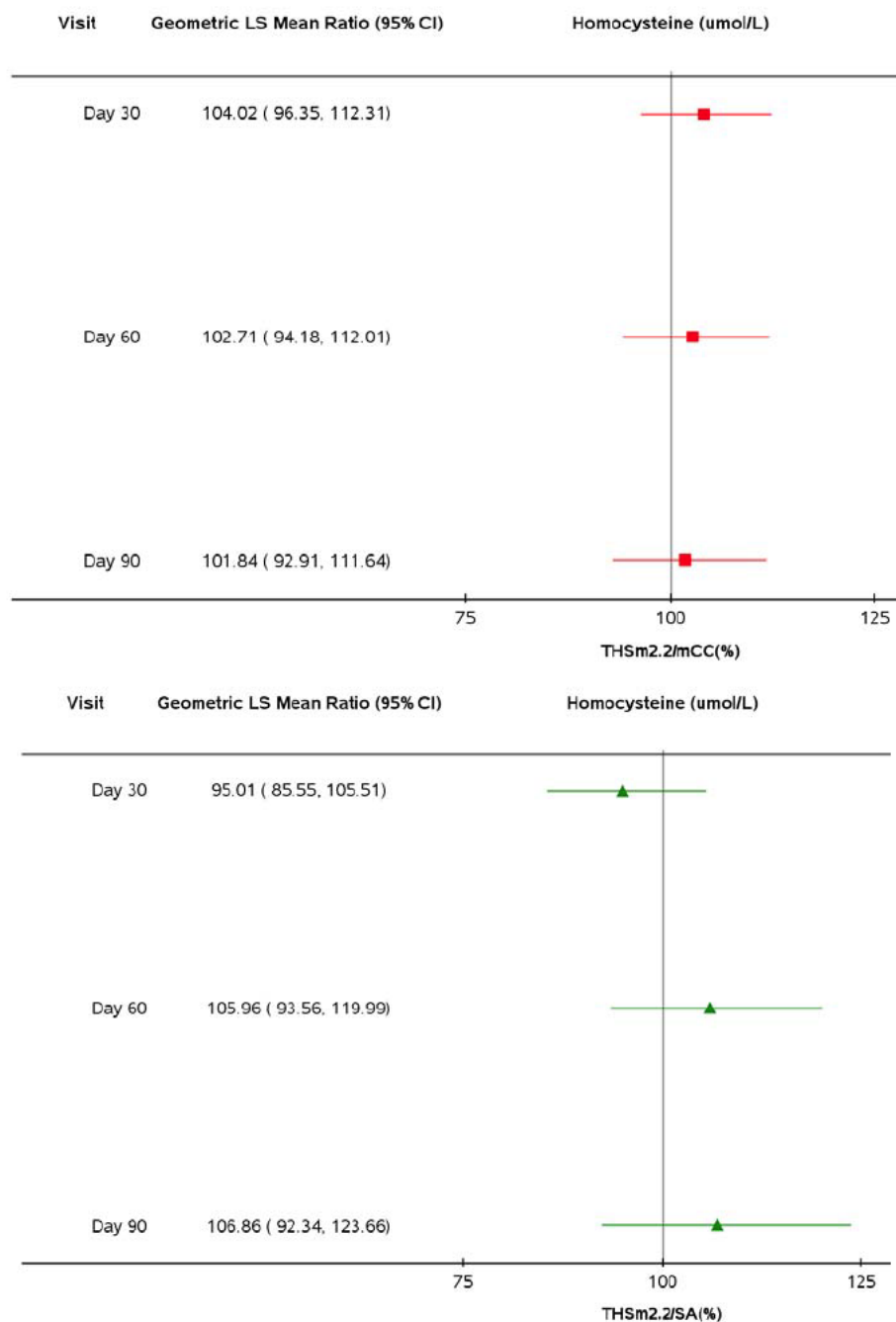
Descriptive statistics of homocysteine and hs-CRP data during the study are provided in [Appendix 15, Table 15.2.4.27.1](#) and [Table 15.2.4.27.2](#) for the PP Set and FAS, respectively, together with percent changes from baseline. Descriptive statistics of fibrinogen data during the study are provided 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 percent 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 versus SA during the study are presented 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 homocysteine, fibrinogen, and hs-CRP are also presented graphically in [Appendix 15, Figure 15.1.2.2](#) and in [Figure 51, Figure 52, and Figure 53](#), respectively.

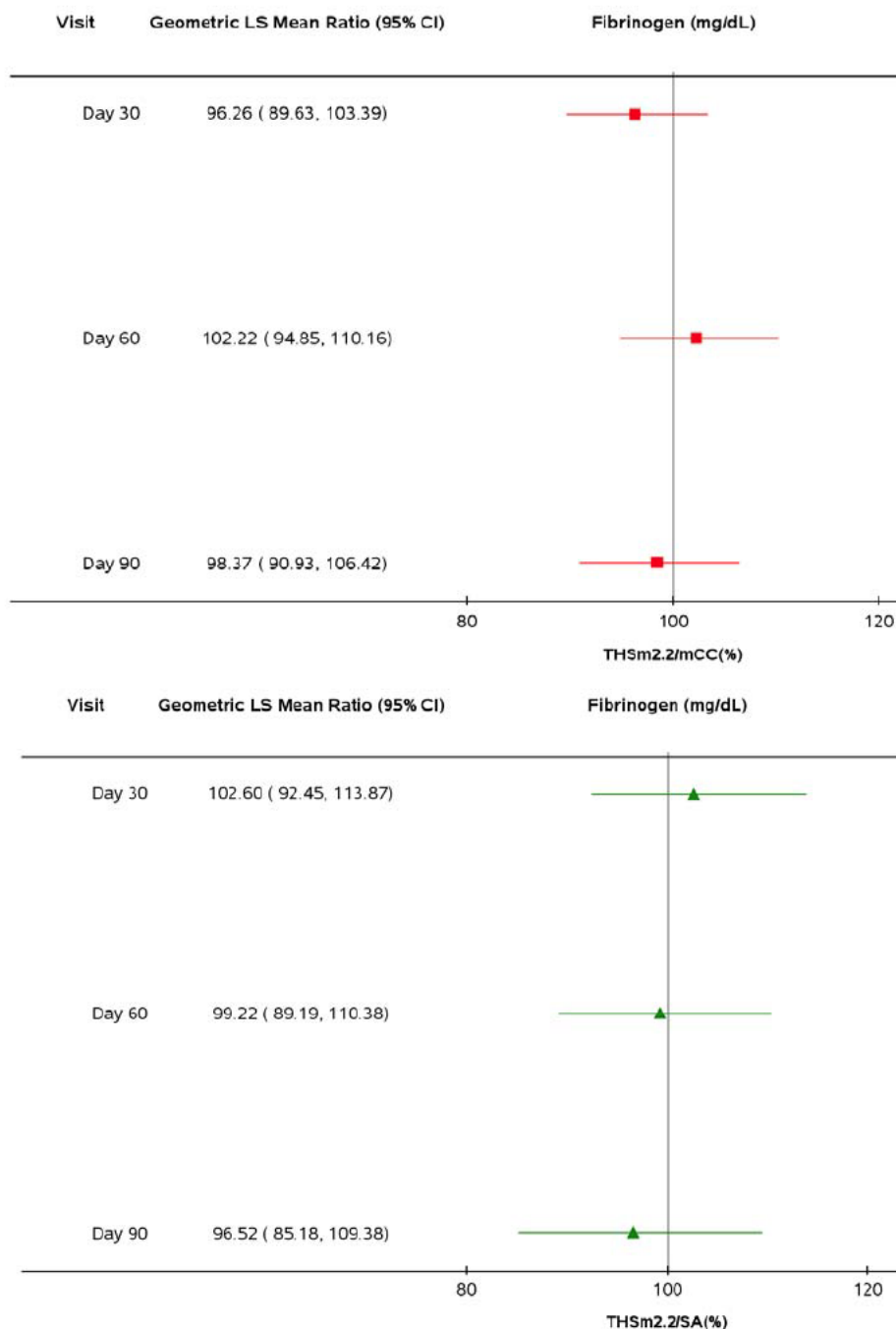




**Figure 51 Forest Plot of Statistical Analysis of Homocysteine ( $\mu\text{mol/L}$ ) During the Course of the Study (PP Set)**

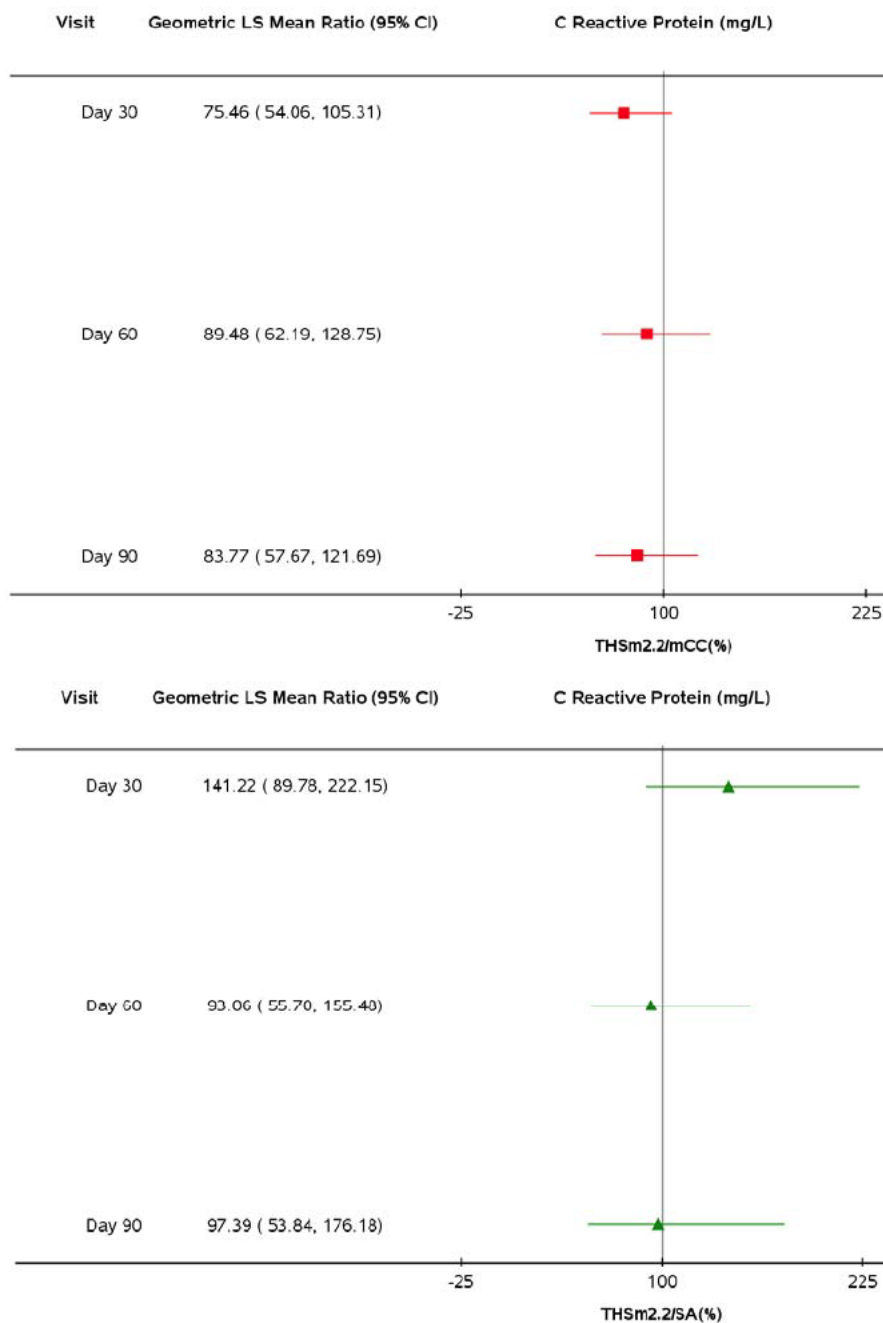


Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.  
Data Source: [Appendix 15, Figure 15.1.2.2.](#)

**Figure 52 Forest Plot of Statistical Analysis of Fibrinogen (mg/dL) During the Course of the Study (PP Set)**

Abbreviations: CI = confidence interval; 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.](#)

**Figure 53 Forest Plot of Statistical Analysis of hs-CRP (mg/L) During the Course of the Study (PP Set)**

Abbreviations: CI = confidence interval; hs-CRP = highly sensitive C-reactive protein; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

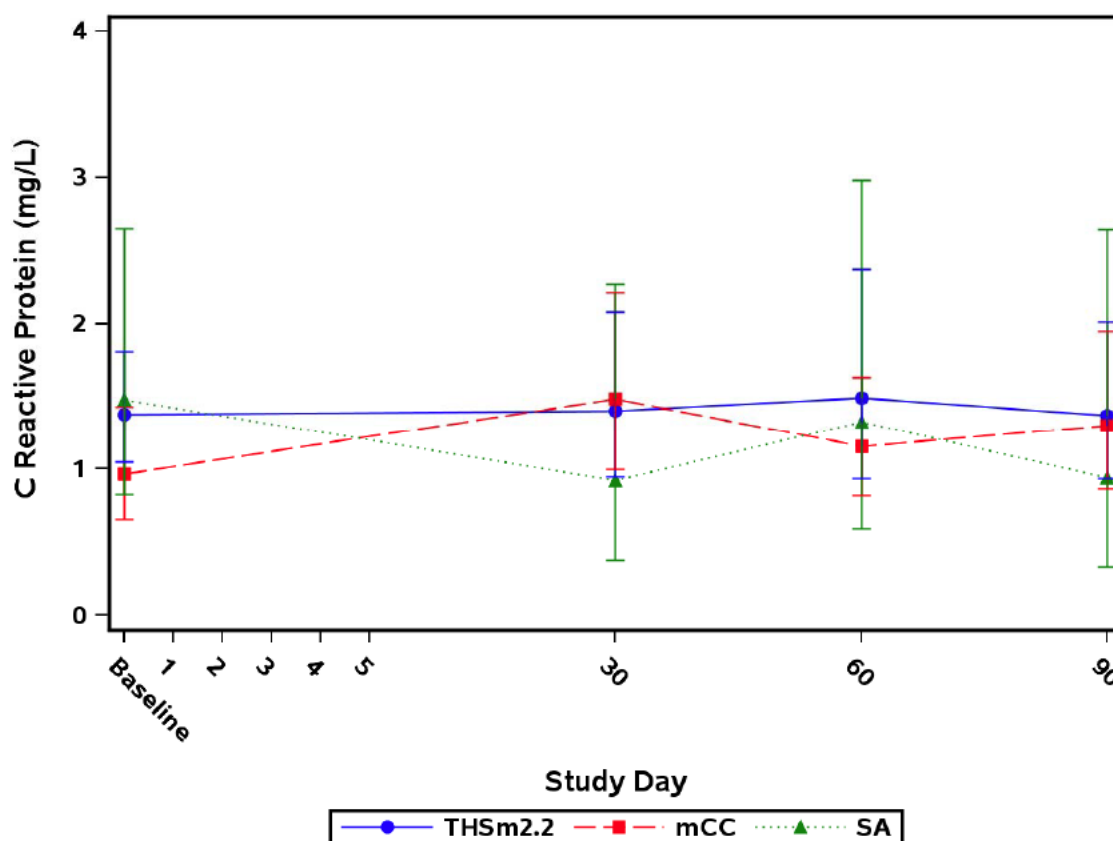
Data Source: [Appendix 15, Figure 15.1.2.2.](#)



For homocysteine and fibrinogen, the mean values were comparable to baseline on Days 30, 60, and 90 for all study arms. There were no notable differences in homocysteine and fibrinogen between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at any time point in the Ambulatory Period, with the 95% CIs for the ratios for all assessments spanning 100% (Figure 51 and Figure 52).

The profile of geometric mean hs-CRP levels during the study is presented in Figure 54.

**Figure 54 Geometric Mean and 95% CIs hs-CRP (mg/dL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; hs-CRP = highly sensitive C-reactive protein; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.3.1.](#)





For hs-CRP, levels were comparable to baseline for the THS 2.2 Menthol arm on Days 30, 60, and 90. In the mCC and SA arms, hs-CRP geometric mean levels fluctuated between approximately 1.0 and 1.5 mg/L. On Day 30, the LS mean of hs-CRP in subjects who switched to THS 2.2 Menthol use was 24.54% lower than that of subjects who continued to smoke mCC although the 95% CIs spanned 100% (95% CI: 54.06, 105.31). There were no notable differences observed on Days 60 and 90.

On Day 30, the LS mean of hs-CRP in subjects who switched to THS 2.2 Menthol use was 41.22% higher than that of subjects who abstained from smoking although the 95% CIs spanned 100% (95% CI: 89.78, 222.15). There were no notable differences observed on Days 60 and 90.

The results for the FAS were consistent with the results for the PP Set for homocysteine, fibrinogen, and hs-CRP.

#### 11.2.6.7 Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure During the Study

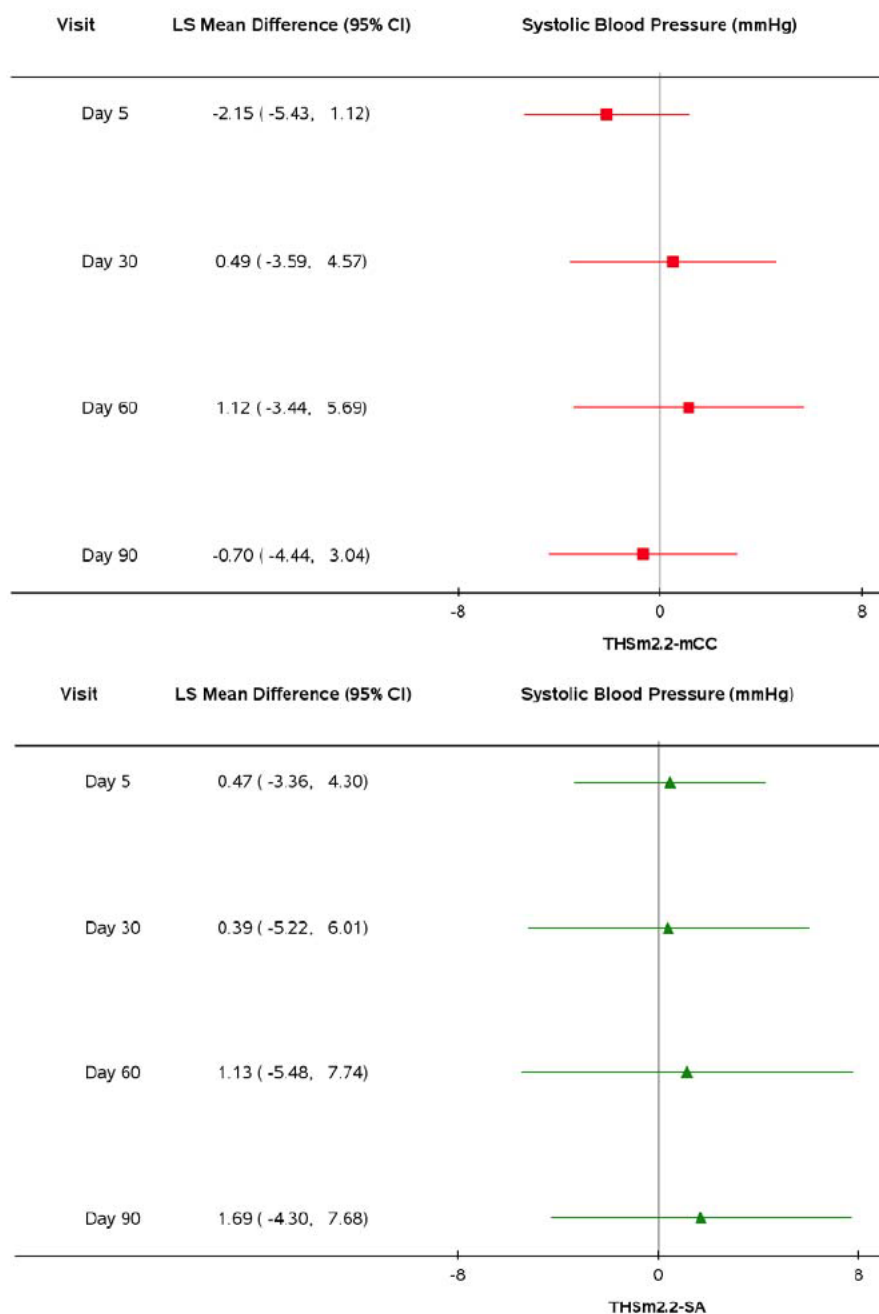
Subject listings of systolic and diastolic blood pressure details are provided in [Appendix 15, Listing 15.3.6.9](#).

Descriptive statistics of systolic and diastolic blood pressure during 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 percent changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#).

Analyses for THS 2.2 Menthol use versus mCC use and SA 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 and are also graphically presented in [Appendix 15, Figure 15.1.2.2](#). The statistical analyses are also presented in [Figure 55](#) and [Figure 56](#).



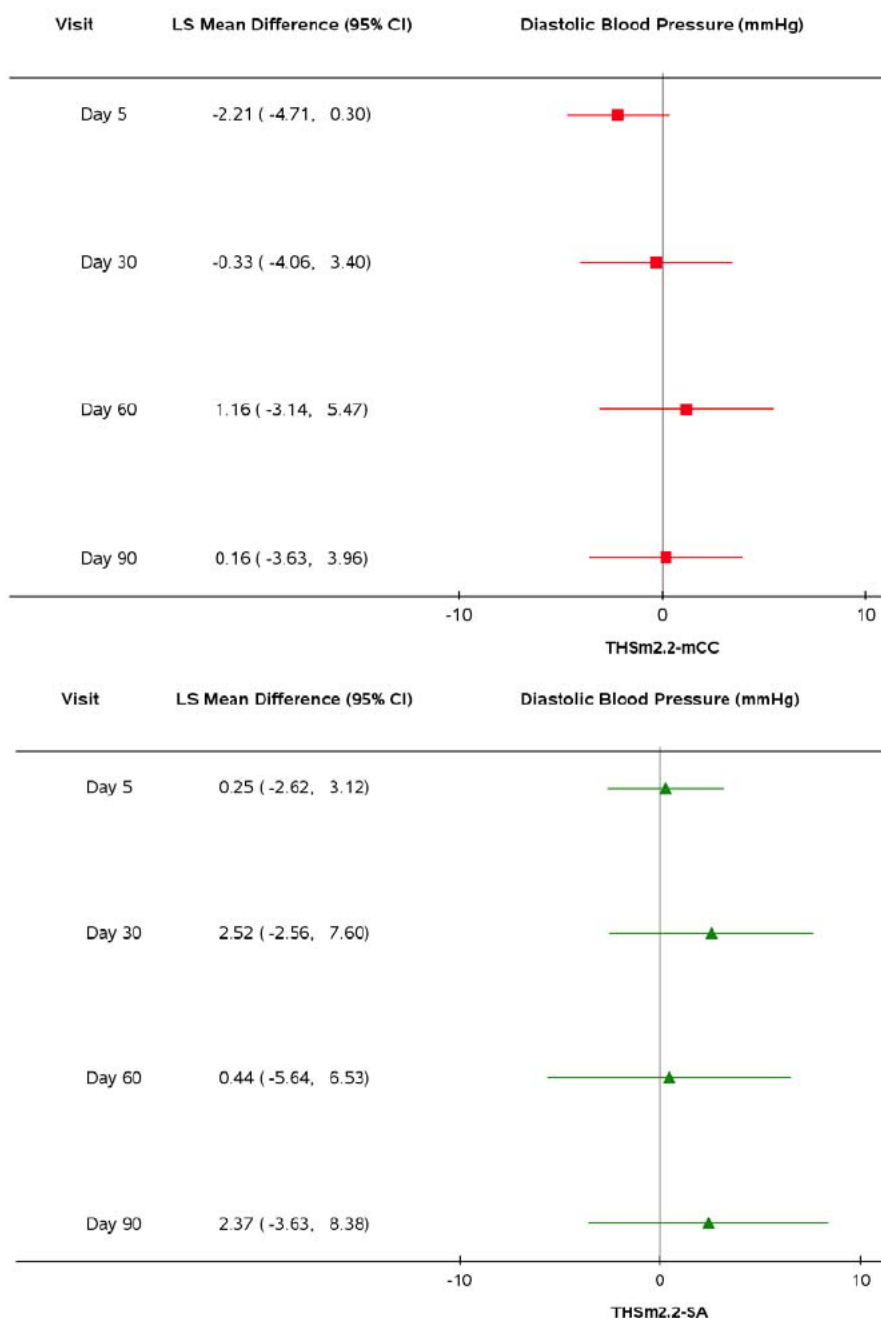
**Figure 55 Forest Plot of Statistical Analysis of Systolic Blood Pressure (mmHg) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.  
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 interval; LS = least squares; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Day 5 assessment shown in the figure was carried out on Day 6.

Data Source: [Appendix 15, Figure 15.1.2.2.](#)



For systolic and diastolic blood pressure, the mean values were comparable to baseline on Days 6, 30, 60, and 90 for all study arms. There were no notable differences in systolic and diastolic blood pressure between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at any time point in the Ambulatory Period, with the 95% CIs for the differences for all assessments spanning 0.

The results for the FAS were consistent with the results for the PP Set for systolic and diastolic blood pressure.

#### 11.2.6.8 Risk Markers of Metabolic Syndrome: Blood Glucose, Hemoglobin A1c, Body Weight, and Waist Circumference During the Study

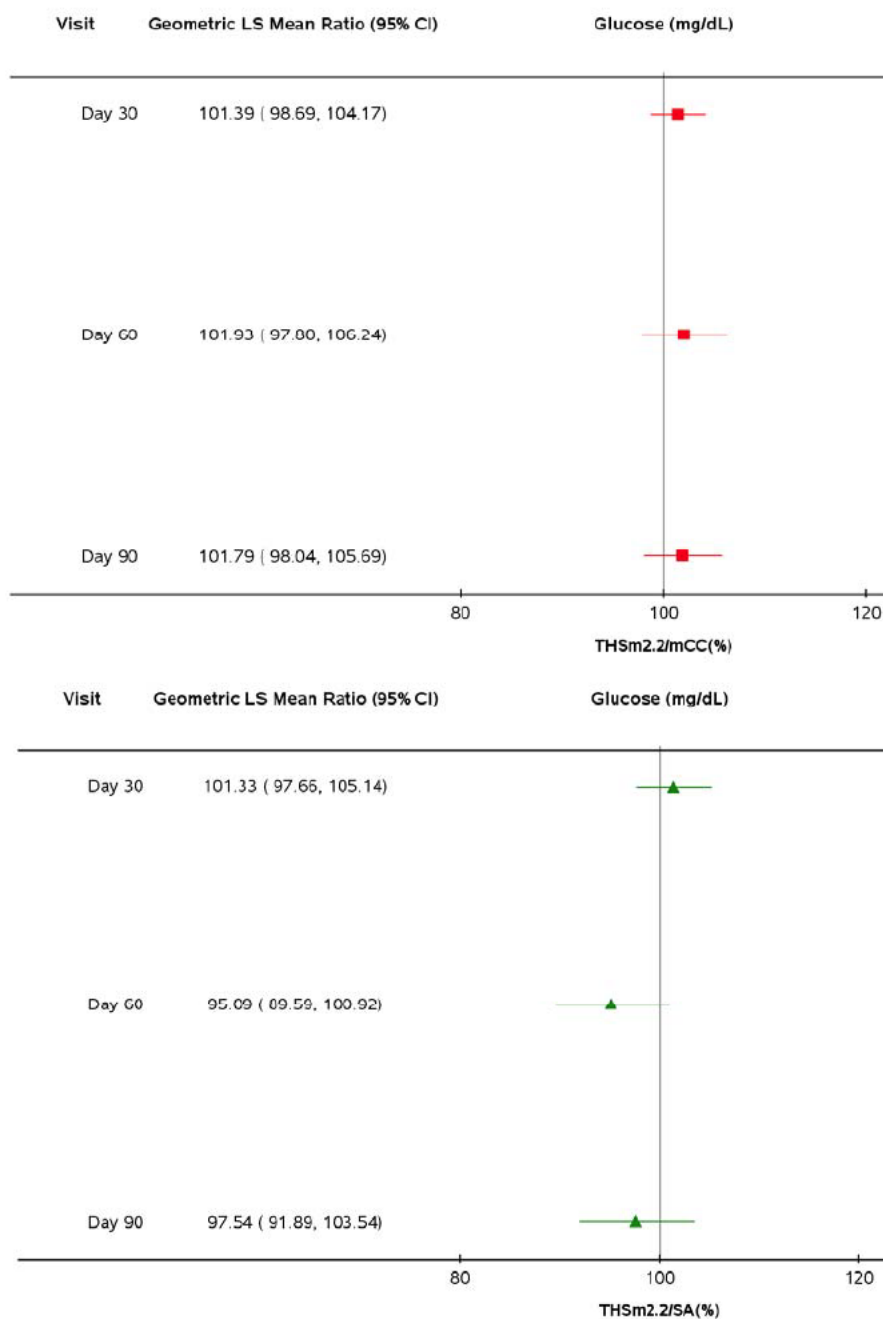
Descriptive statistics of blood glucose during the study are provided in [Appendix 15, Table 15.2.4.27.1](#) and [Table 15.2.4.27.2](#) for the PP Set and FAS, respectively, together with percent changes from baseline. Descriptive statistics of HbA1c at baseline and on Day 90 are provided in [Appendix 15, Table 15.2.4.29.1](#) and [Table 15.2.4.29.2](#) for the PP Set and FAS, respectively, together with percent changes from baseline. 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 percent changes from baseline. The results are also presented graphically in [Appendix 15, Figure 15.1.2.3.1](#).

Analyses for THS 2.2 Menthol use versus mCC use and SA on Days 30, 60, and 90 for blood glucose, and Day 90 for HbA1c, body weight and waist circumference are presented in [Appendix 15, Table 15.2.4.25.1](#) and [Table 15.2.4.25.2](#) for the PP Set and FAS, respectively and are also graphically presented in [Appendix 15, Figure 15.1.2.2](#). The statistical analyses of blood glucose are also presented in [Figure 57](#).





**Figure 57 Forest Plot of Statistical Analysis of Blood Glucose (mg/dL) During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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.](#)



For blood glucose, the geometric mean values were comparable to baseline on Days 30, 60, and 90 for all study arms. There were no notable differences in blood glucose between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at any time point in the Ambulatory Period, with the 95% CIs for the ratios for all assessments spanning 100%.

For HbA1c, the mean values were comparable to baseline on Day 90 for all study arms. There were no notable differences in blood glucose between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC (LS mean difference: -0.04%; 95% CI: -0.16, 0.09). There were also no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking on Day 90 (LS mean difference: 0.14%; 95% CI: -0.05, 0.32).

For body weight, the mean values were comparable to baseline on Day 90 for all study arms. There were no notable differences in body weight between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC (LS mean difference: -0.12 kg; 95% CI: -1.35, 1.12). There were also no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking on Day 90 (LS mean difference: -0.59 kg; 95% CI: -2.60, 1.42).

For waist circumference, the mean values were comparable to baseline on Day 90 for all study arms. There were no notable differences in waist circumference between subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC (LS mean difference: -2.1 cm; 95% CI: -10.2, 6.1). There were also no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking on Day 90 (LS mean difference: 9.3 cm; 95% CI: -3.8, 22.5).

The results for the FAS were consistent with the results for the PP Set for blood glucose, HbA1c, body weight, and waist circumference.

#### 11.2.6.9 Risk Markers for Respiratory Diseases: Lung Function Including Standard Spirometry, Lung Volume, and Gas Transfer

Subject listings of lung function data are provided in [Appendix 15, Listing 15.3.6.11](#).

Descriptive statistics of lung function (including spirometry, lung volume, and gas transfer parameters) are provided in [Appendix 15, Table 15.2.4.70](#) for the PP Set, together with percent changes from baseline to Day 6/Discharge Confinement and Day 91/Discharge Ambulatory. The results are also presented graphically in [Appendix 15, Figure 15.1.2.30](#) for the PP Set. Descriptive statistics of the lung function data have also been presented by the Safety Population, and these results are presented in [Section 12.4.4](#).



Overall on Day 6/Discharge Confinement and on Day 91/Discharge Ambulatory, percent changes from baseline for gas transfer parameters (DLCO and KCO), lung volume parameters (FRV, TLC, VC, and IC), and spirometry parameters (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and MEF 25-75) were small and variable for all study arms.

The gas transfer parameter, DLCO, was increased from baseline on Day 6/Discharge Confinement and further increased on Day 91/Discharge Ambulatory in the THS 2.2 Menthol arm; whereas an increase from baseline in DLCO was only apparent at Day 91/Discharge Ambulatory in the mCC arm. For KCO, changes from baseline on Day 6/Discharge Confinement were minimal for all study arms; although an increase from baseline was observed on Day 91/Discharge Ambulatory for the THS 2.2 Menthol arm.

For lung volume parameters, FRV, TLC, and VC, decreases from baseline were observed for the THS 2.2 Menthol and mCC arms on Day 91/Discharge Ambulatory; mean decreases from baseline were lower in the THS 2.2 Menthol arm compared to the mCC arm for TLC and VC. The IC parameter values were increased from baseline for the THS 2.2 Menthol and mCC arms on Day 6/Discharge Confinement and for the THS 2.2 Menthol arm on Day 91/Discharge Ambulatory; whereas decreases from baseline were observed on both days for the SA arm.

Spirometry parameter, MEF 25-75 was increased from baseline on Day 6/Discharge/Confinement and Day 91/Discharge Ambulatory for all study arms, with a greater increase from baseline observed for the mCC arm. The percent of predicted FEV<sub>1</sub> and FVC values were decreased from baseline on Day 91/Discharge Ambulatory for all study arms, with a greater decrease from baseline observed in the mCC arm compared to the THS 2.2 Menthol and SA arms. The changes from baseline for the ratio of FEV<sub>1</sub>/FVC for all study arms was minimal.

Analyses for THS 2.2 Menthol use versus mCC use, and versus SA during the study are presented in [Appendix 15, Table 15.2.4.71](#) and in [Table 110](#) for the PP Set.

**Table 110 Analysis of Full Lung Function Results (PP Set)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference (95% CI)	THS m2.2 – SA Difference (95% CI)
DLCO (mL/min/mmHg)	Day 6	THS m2.2	74	23.69		
		mCC	34	23.08	0.61 (-0.25, 1.47)	0.16 (-0.85, 1.18)
		SA	21	23.53		
	Day 91	THS m2.2	47	24.56		
		mCC	30	24.25	0.31 (-1.09, 1.72)	1.95 (-0.33, 4.22)
		SA	8	22.61		
KCO (mmol/min/kPa/L)	Day 6	THS m2.2	71	1.37		
		mCC	34	1.35	0.02 (-0.03, 0.07)	0.00 (-0.06, 0.06)
		SA	21	1.36		
	Day 91	THS m2.2	45	1.41		
		mCC	30	1.36	0.05 (-0.02, 0.12)	0.04 (-0.09, 0.16)
		SA	7	1.38		
FEV <sub>1</sub> (L) with bronchodilator	Day 6	THS m2.2	71	3.44		
		mCC	34	3.41	0.03 (-0.06, 0.12)	-0.11 (-0.21, -0.02)
		SA	23	3.56		
	Day 91	THS m2.2	47	3.45		
		mCC	30	3.41	0.05 (-0.06, 0.15)	0.02 (-0.14, 0.18)
		SA	9	3.43		



**Table 110 Analysis of Full Lung Function Results (PP Set) (Continued)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference (95% CI)	THS m2.2 – SA Difference (95% CI)
FEV <sub>1</sub> (pred%) with bronchodilator	Day 6	THS m2.2	71	93.22		
		mCC	34	92.9	0.32 (-2.46, 3.10)	-3.05 (-6.24, 0.13)
		SA	23	96.27		
	Day 91	THS m2.2	45	91.18		
		mCC	30	90.64	0.53 (-2.79, 3.85)	-1.46 (-6.63, 3.71)
		SA	9	92.64		
FVC (L) with bronchodilator	Day 6	THS m2.2	74	4.34		
		mCC	34	4.34	-0.01 (-0.08, 0.09)	-0.05 (-0.14, 0.04)
		SA	23	4.39		
	Day 91	THS m2.2	47	4.37		
		mCC	30	4.32	0.05 (-0.05, 0.15)	0.04 (-0.11, 0.19)
		SA	9	4.34		
FVC (pred%) with bronchodilator	Day 6	THS m2.2	74	95.46		
		mCC	34	94.5	0.97 (-1.26, 3.19)	-1.22 (-3.75, 1.31)
		SA	23	96.68		
	Day 91	THS m2.2	47	93.81		
		mCC	30	93.36	0.46 (-2.09, 3.00)	-1.26 (-5.20, 2.68)
		SA	9	95.07		

**Table 110 Analysis of Full Lung Function Results (PP Set) (Continued)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference (95% CI)	THS m2.2 – SA Difference (95% CI)
FEV <sub>1</sub> /FVC ratio	Day 6	THS m2.2	74	0.79		
		mCC	34	0.79	0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.01)
		SA	23	0.81		
	Day 91	THS m2.2	47	0.79		
		mCC	30	0.79	0.00 (-0.02, 0.02)	-0.01 (-0.04, 0.02)
		SA	9	0.8		
MEF 25-75 (L/s) with bronchodilator	Day 6	THS m2.2	74	3.32		
		mCC	34	3.28	0.04 (-0.21, 0.30)	-0.08 (-0.37, 0.21)
		SA	23	3.4		
	Day 91	THS m2.2	47	5.21		
		mCC	30	5.88	-0.67 (-6.33, 4.99)	1.23 (-7.62, 10.07)
		SA	9	3.99		
TLC (L)	Day 6	THS m2.2	74	5.95		
		mCC	34	6.07	-0.12 (-0.63, 0.39)	-0.10 (-0.69, 0.48)
		SA	23	6.05		
	Day 91	THS m2.2	47	5.78		
		mCC	30	5.69	0.09 (-0.25, 0.43)	0.39 (-0.13, 0.92)
		SA	9	5.38		

**Table 110 Analysis of Full Lung Function Results (PP Set) (Continued)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC Difference (95% CI)	THS m2.2 – SA Difference (95% CI)
FRV(L)	Day 6	THS m2.2	74	2.89		
		mCC	34	3.1	-0.21 (-0.69, 0.27)	-0.28 (-0.83, 0.28)
		SA	23	3.16		
	Day 91	THS m2.2	47	2.8		
		mCC	30	2.89	-0.09 (-0.31, 0.13)	-0.42 (-0.76, -0.07)
		SA	9	3.21		
IC (L)	Day 6	THS m2.2	74	3.07		
		mCC	34	2.98	0.10 (-0.10, 0.30)	0.19 (-0.04, 0.42)
		SA	23	2.89		
	Day 91	THS m2.2	47	3.01		
		mCC	30	2.79	0.21 (-0.08, 0.51)	0.88 (0.43, 1.33)
		SA	9	2.13		
VC (L)	Day 6	THS m2.2	74	4.43		
		mCC	34	4.38	0.05 (-0.03, 0.13)	0.00 (-0.09, 0.09)
		SA	23	4.43		
	Day 91	THS m2.2	47	4.43		
		mCC	30	4.33	0.10 (0.00, 0.21)	0.05 (-0.10, 0.21)
		SA	9	4.38		



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Abbreviations: DLCO = diffusion capacity for lung CO; FEV<sub>1</sub> = forced expiratory volume in 1 second; FRV = forced residual volume; FVC = forced vital capacity; IC = inspiratory capacity; KCO = rate constant of CO; mCC = Menthol conventional cigarette; MEF = mid expiratory flow; N = number of subjects in arm; n = number of subject; THS m2.2 = Tobacco Heating System 2.2 Menthol; TLC = total lung capacity; VC = vital capacity.

Data Source: [Appendix 15](#), [Tables 15.2.4.71](#).





There were no notable differences on Day 6/Discharge Confinement and Day 91/Discharge Ambulatory in gas transfer parameters (DLCO and KCO), lung volume parameters (FRV, TLC, and IC), or spirometry parameters (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and MEF 25-75) between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. On Day 91/Discharge Ambulatory, VC was 0.10 L higher in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC (95% CI: 0.00, 0.21).

Between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking there were no notable differences on Day 6/Discharge Confinement and Day 91/Discharge Ambulatory in gas transfer parameters (DLCO and KCO), lung volume parameters (VC, TLC, and IC), or spirometry parameters (FVC, FEV<sub>1</sub>/FVC, and MEF 25-75). On Day 6/Discharge Confinement, FEV<sub>1</sub> was 0.11 L lower in subjects who switched to THS 2.2 Menthol compared to subjects who abstained from smoking (95% CI: 0.02, 0.21) but there was no difference on Day 91/Discharge Ambulatory. On Day 91/Discharge Ambulatory the FRV was 0.42 L (95% CI: 0.07, 0.76) lower while the inspiratory capacity was 0.88L (95% CI: 0.43, 1.33) higher in subjects who switched to THS 2.2 Menthol compared to subjects who abstain from smoking.

### 11.3 Analysis of Exploratory Endpoints

#### 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 percent change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.64.1](#) and [Table 15.2.4.64.2](#) for the PP Set and FAS, respectively. Data for the PP Set at baseline and Day 5 are also provided in [Table 111](#) for the Confinement Period and in [Table 112](#) for the Ambulatory Period.

**Table 111 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (REV/24h) During the Confinement Period (PP Set)**

Study Arm	Time Point	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Baseline	63	30251.24	29094.282	2416.2	19463.24	148367.2
	Day 5	73	8438.27	9523.211	0.0	5800.74	43350.4
mCC	Baseline	29	24798.69	19446.807	0.0	17384.40	81244.2
	Day 5	34	36544.33	29684.109	0.0	30608.70	129114.4
SA	Baseline	21	28259.41	18515.293	5611.2	25823.00	80368.2
	Day 5	23	10806.29	17858.405	0.0	3920.18	80368.2

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 15.2.4.64.1](#).

At baseline, mean Ames mutagenicity test values were consistent between the THS 2.2 Menthol and SA arms (30251.24 and 28259.41 REV/24h, respectively) and lower in the mCC arm (24798.69 REV/24h). On Day 5, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values had decreased by approximately 72% and 62%, respectively. In the mCC arm, Ames mutagenicity test values (REV/24h) showed a mean increase from baseline of approximately 47% ([Table 111](#)). Consistent results were also observed in median values, with Day 5 values of 70% and 85% lower than baseline in the THS 2.2 Menthol and SA arms, respectively, and 76% higher than baseline in the mCC arm.

**Table 112 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (REV/24h) During the Ambulatory Period (PP Set)**

Study Arm	Time Point	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS m2.2	Baseline	41	28352.92	29045.675	2416.2	18668.75	148367.2
	Day 90	47	10308.49	8808.979	0.0	7439.08	53250.4
mCC	Baseline	28	23283.64	17577.460	0.0	17131.64	81244.2
	Day 90	32	28405.28	21825.957	5968.1	22047.46	87139.8
SA	Baseline	8	22469.69	10997.892	6900.5	24980.40	35294.0
	Day 90	9	6322.92	4817.130	0.0	6178.08	13607.2

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 15.2.4.64.1](#).

On Day 90, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values were approximately 64% and 72% lower than baseline, respectively; while in the mCC arm, mean Ames mutagenicity test values were approximately 22% higher than baseline ([Table 112](#)). Consistent results were also observed in median values, with values approximately 60% and 75% lower than baseline on Day 90 in the THS 2.2 Menthol and SA arms, respectively, and 29% higher in the mCC arm.

The results for the FAS were consistent with the results for the PP Set.

### 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 15.3.6.20](#). Descriptive statistics of CYP2A6 activity including percent change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.62.1](#) and [Table 15.2.4.62.2](#) for the PP Set and FAS, respectively. Data for the PP Set are provided in [Table 113](#). 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 15.2.4.62.1.1](#) and [Table 15.2.4.62.2.1](#) for the PP Set and FAS, respectively.

**Table 113 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 6 % change from baseline	74	12.504	29.7513	-31.72	8.529	124.00
mCC	Day 6 % change from baseline	35	6.809	26.4220	-31.80	0.941	91.80
SA	Day 6 % change from baseline	23	180.452	120.6736	43.27	157.591	486.11

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. % 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 15.2.4.62.1](#).

At baseline, CYP2A6 activity was comparable between study arms (range of 28.02% to 30.07%). In the THS 2.2 Menthol and mCC arms, CYP2A6 increased by approximately 13% and 7%, respectively, on Day 6/Discharge Confinement. In the SA arm, CYP2A6 activity increased by approximately 1.80-fold. Comparable changes from baseline were observed when subject assessments with concomitant medication affecting CYP2A6 activity were excluded. This affected 4, 1, and 0 subjects in the THS 2.2 Menthol, mCC, and SA arms, respectively, on Day 6/Discharge Confinement.

Analyses of CYP2A6 activity (absolute) on Day 6/Discharge Confinement for THS 2.2 Menthol use versus mCC use, and versus SA, are tabulated in [Appendix 15, Table 15.2.4.63.1](#) and [Table 15.2.4.63.2](#), for the PP Set and FAS, respectively. In addition, analyses excluding any assessments taken within 5 half-lives of a concomitant medication known to impact CYP2A6 activity are presented in [Appendix 15, Table 15.2.4.63.1.1](#) and [15.2.4.63.2.1](#) for the PP Set and FAS, respectively.

Data for the PP Set on Day 6/Discharge Confinement are presented in [Table 114](#).



**Table 114 Analysis of CYP2A6 Activity (%) versus mCC and SA on Day 6 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV (%)	95% CI
				(THS m2.2:mCC) (%)		
Day 6/Discharge Confinement	THS m2.2	74	32.802	105.68	25.58	95.19, 117.33
	mCC	33	31.039			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV (%)	95% CI
				(THS m2.2:SA) (%)		
Day 6/Discharge Confinement	THS m2.2	74	32.802	42.53	25.58	37.74, 47.92
	SA	23	77.131			

Abbreviations: 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 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 15.2.4.63.1](#).

There was no notable difference in absolute CYP2A6 activity on Day 6/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 Day 6/Discharge Confinement, the absolute CYP2A6 activity following THS 2.2 Menthol use was 57.47% lower than the activity in subjects who abstained from smoking (95% CI: 52.08, 62.26).

The results from FAS and the analysis excluding subject assessments with concomitant medication affecting CYP2A6 activity were comparable to the results presented above.

Percent change from baseline data for the PP Set on Day 90 are presented in [Table 115](#).

**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	47		10.905		37.6735	-31.13	3.967	174.06
mCC	Day 90 % change from baseline	32		13.261		27.5103	-34.74	11.270	98.11
SA	Day 90 % change from baseline	9		110.910		188.9485	0.08	38.550	588.21

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. % 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 15.2.4.62.1](#).

At baseline for the PP Set, CYP2A6 activity was comparable between study arms (range of 26.24% to 30.11%). In the THS 2.2 Menthol and mCC arms, CYP2A6 increased by approximately 11% and 13% on Day 90, respectively. In the SA arm, CYP2A6 activity increased by approximately 1.10-fold (median of 38.55%).

The analysis excluding assessments within 5 half-lives of concomitant medications that impact CYP2A6 activity showed consistent results, with only 2 subjects excluded from the THS 2.2 Menthol arm and 1 subject from the SA arm.

Analyses of CYP2A6 activity on Day 90 for the PP Set are also provided in [Table 116](#).

**Table 116 Analysis of CYP2A6 Activity (%) 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 (%)		
Day 90	THS m2.2	47	30.471	93.16	29.61	81.39, 106.63	
	mCC	31	32.709				

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			95% CI
					CV (%)		
Day 90	THS m2.2	47	30.471	62.73	29.61	50.70, 77.61	
	SA	9	48.577				

Abbreviations: 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 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 15.2.4.63.1](#).

There was no notable difference in 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 CYP2A6 activity following THS 2.2 Menthol use was 37.27% lower than the activity in subjects who abstained from smoking (95% CI: 22.39, 49.30).

### 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 15.3.6.13](#).

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 15.2.4.51.1](#), [Table 15.2.4.51.2](#), and [Table 15.2.4.51.3](#), respectively. Data presented in this section are for the PP Set.

**Table 117 Fagerström Test of Nicotine Dependence (PP Set Period 4)**

Time point FTND Score	Statistic	Study Arm		
		THS m2.2 (N=47)	mCC (N=32)	SA (N=9)
Baseline				
	N	47	32	9
	Mean	5.83	5.63	5.89
	SD	2.220	1.700	2.369
	Median	6.00	6.00	6.00
	Min, Max	1.0, 10.0	1.0, 9.0	2.0, 8.0
Mild (n [%])		7 (14.9)	3 (9.4)	2 (22.2)
Moderate (n [%])		19 (40.4)	20 (62.5)	3 (33.3)
Severe (n [%])		21 (44.7)	9 (28.1)	4 (44.4)
Day 90				
	N	46	27	4
	Mean	5.00	4.93	1.50
	SD	2.310	1.839	1.291
	Median	5.00	5.00	1.50
	Min, Max	1.0, 9.0	2.0, 9.0	0.0, 3.0
Mild (0 – 3), n(%)		14 (29.8)	5 (15.6)	4 (44.4)
[1] Mild to Mild, n(%)		5 (10.7)	1 (3.1)	2 (22.2)
[1] Moderate to Mild, n(%)		9 (19.1)	4 (12.5)	1 (11.1)
[1] Severe to Mild, n(%)		0	0	1 (11.1)
Moderate (4 – 6), n(%)		20 (42.6)	18 (56.3)	0
[1] Mild to Moderate, n(%)		2 (4.3)	2 (6.3)	0
[1] Moderate to Moderate, n(%)		7 (14.9)	10 (31.2)	0
[1] Severe to Moderate, n(%)		11 (23.4)	6 (18.8)	0
Severe (7 – 10), n(%)		12 (25.5)	4 (12.5)	0
[1] Moderate to Severe, n(%)		2 (4.3)	2 (6.3)	0
[1] Severe to Severe, n(%)		10 (21.2)	2 (6.2)	0

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 15.2.4.51.1](#).

Within the PP Set on Day 90, the majority of subjects in the THS 2.2 Menthol and the mCC arms reported a moderate dependence on nicotine at baseline (40.4% and 62.5%, respectively) and a moderate dependence on nicotine on Day 90 (42.6% and 56.3%, respectively). A decrease in FTND severity was observed for a number of subjects in both





the THS 2.2 Menthol and mCC arms, with 9 subjects (19.1%) in the THS 2.2 Menthol arm and 4 subjects (12.5%) in the mCC arm shifting from moderate to mild dependency, and 11 subjects (23.4%) in the THS 2.2 Menthol arm and 6 subjects (18.8%) in the mCC arm shifting from severe to moderate dependency. Four subjects in each of the THS 2.2 Menthol and mCC arms reported a worsening of nicotine dependence on Day 90, with 2 subjects (4.3%) in the THS 2.2 Menthol arm and 2 subjects (6.3%) in the mCC arm shifting from mild to moderate, and 2 subjects in the THS 2.2 Menthol arm and 2 subjects in the mCC arm shifting from moderate to severe. There were only 4 subjects with FTND data in the SA arm for the PP Set on Day 90, with all subjects categorized as mild. There were a number of subjects in the SA arm on Day 90 that did not complete the FTND questionnaire in error.

Similar results were also observed for the Compliant Population and for the THS 2.2 Menthol and mCC arms of the FAS. For the SA arm of the FAS, the majority of subjects reported a moderate dependence on nicotine at baseline (18 subjects, 46.2%) and a mild dependence on nicotine on Day 90 (18 subjects, 46.2%). Sixteen subjects in the SA arm of the FAS reported a decrease in FTND severity on Day 90, with 9 subjects (23.1%) shifting from moderate to mild, 4 subjects (10.3%) shifting from severe to mild, and 3 subjects (7.7%) shifting from severe to moderate. Two subjects reported an increase in FTND severity, with 1 subject (2.6%) each reporting a shift from mild to severe and from moderate to severe.

### 11.3.4 Subjective Effects of Smoking Endpoints During the Study

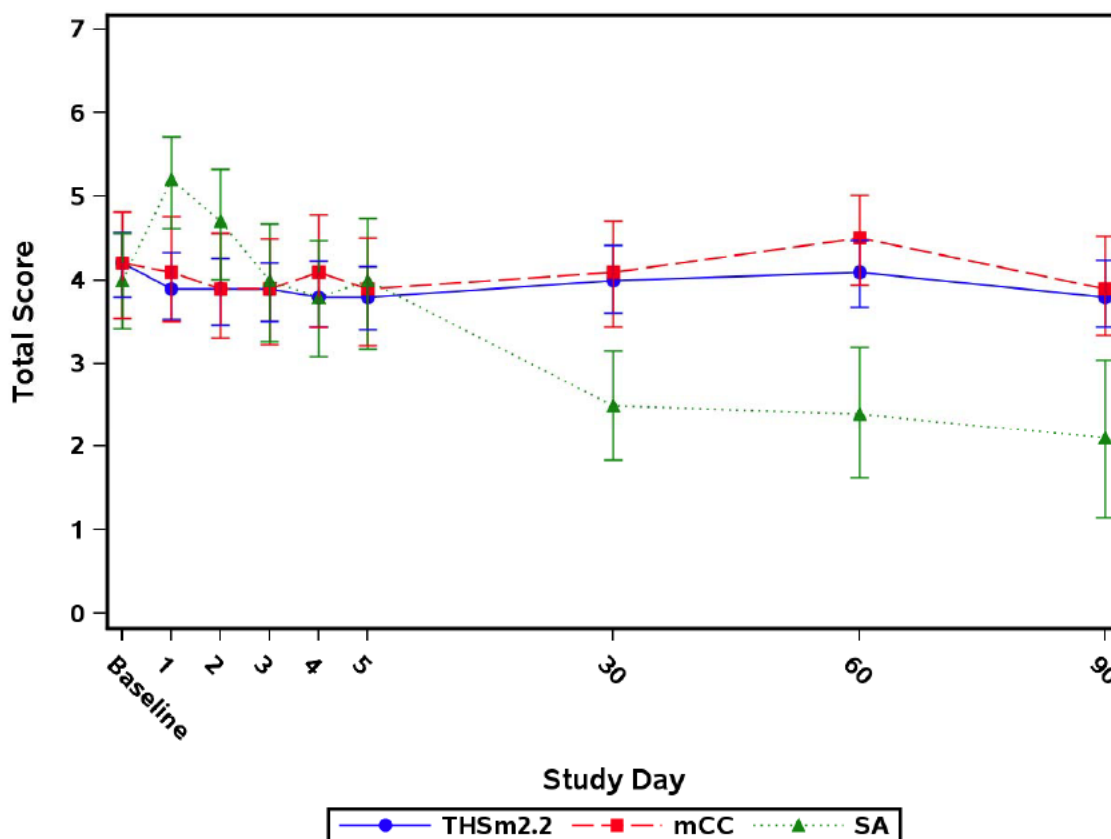
#### 11.3.4.1 Urge-to-Smoke Symptoms (QSU-brief) During the Study

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 15.3.6.14](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.52.1](#) and [Table 15.2.4.52.2](#) for the PP Set and 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 [Figure 15.1.2.4.2](#) for the PP Set and FAS, respectively and [Figure 15.1.2.5.1](#) for the LS means differences. Data for the PP Set are also provided in [Figure 58](#).



**Figure 58 Arithmetic Mean and 95% CI Total Scores for QSU-Brief During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was 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 average urge-to-smoke total scores were 4.19 for the THS 2.2 Menthol arm, 4.17 for the mCC arm, and 3.99 for the SA arm at baseline. For the THS 2.2 Menthol and mCC arms, the average urge-to-smoke total scores remained stable over the 5 days of the Confinement Period (3.78 to 3.93 for the THS 2.2 Menthol arm and 3.86 to 4.13 for the mCC arm; ranges of individual scores were 1.0 to 7.0 for both arms). In the SA arm, the urge-to-smoke total score increased from baseline to Day 1 (score of 5.16, corresponding to an increase of 52.64%). Total score value then slowly decreased and was comparable to the THS 2.2 Menthol and mCC arms on Day 5 (score of 3.95).

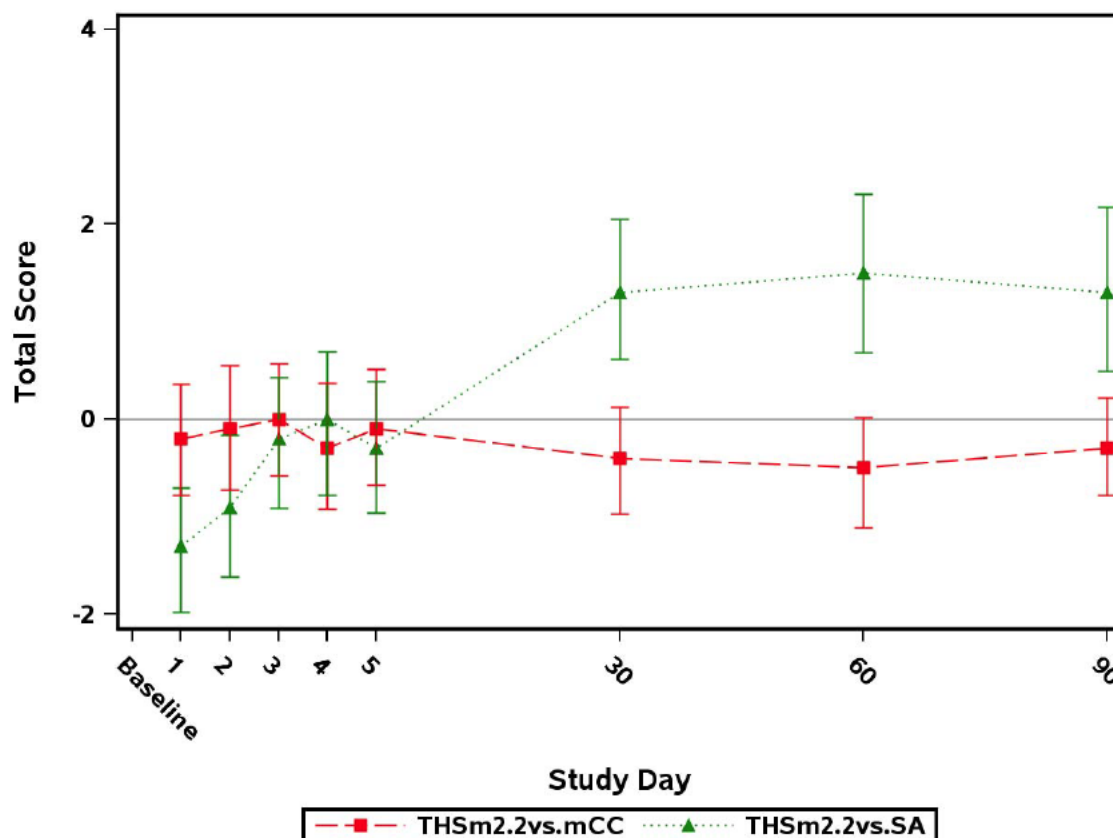


During the Ambulatory Period, the mean urge-to-smoke total scores remained stable and comparable to baseline over the 90 days of the Ambulatory Period for the THS 2.2 Menthol and mCC arms, with Day 90 values of 3.84 and 3.93, respectively. In the SA arm, following increases from baseline in the urge-to-smoke scores during the Confinement Period, the urge-to-smoke total score was decreased from baseline on Day 30 (-41.37%), with a -40.13% decrease on Day 90.

The results from the statistical analysis of the QSU-brief questionnaire factors and total score are tabulated in [Appendix 15, Table 15.2.4.53.1](#) and [Table 15.2.4.53.2](#) for the PP Set and FAS, respectively. Data for the PP Set on Day 5 are presented in [Table 118](#). 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 59](#) for the PP Set.



**Figure 59 Mean and 95% CI Total Scores Least Squares Means Differences for QSU-Brief During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was 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 15.1.2.5.1](#).

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 -0.21 on Day 1 and -0.08 on Day 5. The LS mean differences of THS 2.2 Menthol – SA for urge-to-smoke total scores increased from -1.35 on Day 1 to -0.29 on Day 5 ([Figure 59](#)).

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 -0.29 on Day 90. Whereas, the mean LS mean differences of THS 2.2 Menthol – SA for urge-





to-smoke total scores were 1.33, 1.50, and 1.33 on Days 30, 60, and 90, respectively (Figure 59).

**Table 118 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	3.76	-0.08	-0.68, 0.52
		mCC	34	3.84		
Factor 1	Day 5	THS m2.2	75	4.38	0.14	-0.60, 0.87
		mCC	34	4.24		
Factor 2	Day 5	THS m2.2	75	3.14	-0.29	-0.84, 0.26
		mCC	34	3.43		

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	3.76	-0.29	-0.97, 0.40
		SA	24	4.04		
Factor 1	Day 5	THS m2.2	75	4.38	-0.45	-1.27, 0.38
		SA	24	4.82		
Factor 2	Day 5	THS m2.2	75	3.14	-0.15	-0.77, 0.47
		SA	24	3.29		

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 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 15.2.4.53.1](#).

Considering the overall and individual time points, there were no notable differences between the LS means QSU-brief urge-to-smoke total scores, Factor 1 scores, or Factor 2 scores on Day 5 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.



There were no notable differences between the LS means QSU-brief urge-to-smoke total scores, Factor 1 scores, or Factor 2 scores on Day 5 for the subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking, with 95% CIs for all parameters spanning 0.

The results for the FAS were consistent with the results for the PP Set.

Data for the PP Set on Day 90 are presented in [Table 119](#).

**Table 119 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	46	3.74	-0.29	-0.79, 0.22
		mCC	27	4.02		
Factor 1	Day 90	THS m2.2	46	4.46	-0.25	-0.87, 0.37
		mCC	27	4.72		
Factor 2	Day 90	THS m2.2	46	3.00	-0.33	-0.83, 0.17
		mCC	27	3.33		

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Total	Day 90	THS m2.2	46	3.74	1.33	0.48, 2.18
		SA	7	2.41		
Factor 1	Day 90	THS m2.2	46	4.46	1.73	0.70, 2.77
		SA	7	2.73		
Factor 2	Day 90	THS m2.2	46	3.00	0.89	0.04, 1.74
		SA	7	2.11		

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 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 15.2.4.53.1](#).

Considering the overall and individual time points, there were no notable differences between the LS means QSU-brief urge-to-smoke total scores, Factor 1 scores, or Factor 2 scores on Day 90 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 during the Ambulatory Period.

The urge-to-smoke overall and factor scores for subjects who switched to THS 2.2 Menthol use were higher than those of subjects who abstained from smoking, with LS mean differences on Day 90 of 1.33 points (95% CI: 0.48, 2.18), 1.73 points (95%



CI: 0.70, 2.77), and 0.89 points (95% CI: 0.04, 1.74) for QSU-brief total score, Factor 1 score, and Factor 2 score, respectively.

The results for the FAS were consistent with the results for the PP Set although the differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking were smaller than for the PP Set; with LS mean differences on Day 90 of 0.74 points (95% CI: 0.19, 1.28), 0.89 points (95% CI: 0.22, 1.56), and 0.54 points (95% CI: 0.04, 1.04) for QSU-brief total score, Factor 1 score, and Factor 2 score, respectively.

#### 11.3.4.2 MNWS-R During the Study

Responses to the MNWS-R questionnaire results are listed by subject in [Appendix 15, Listing 15.3.6.15](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.56.1](#) and [Table 15.2.4.56.2](#) for the PP Set and FAS, respectively.

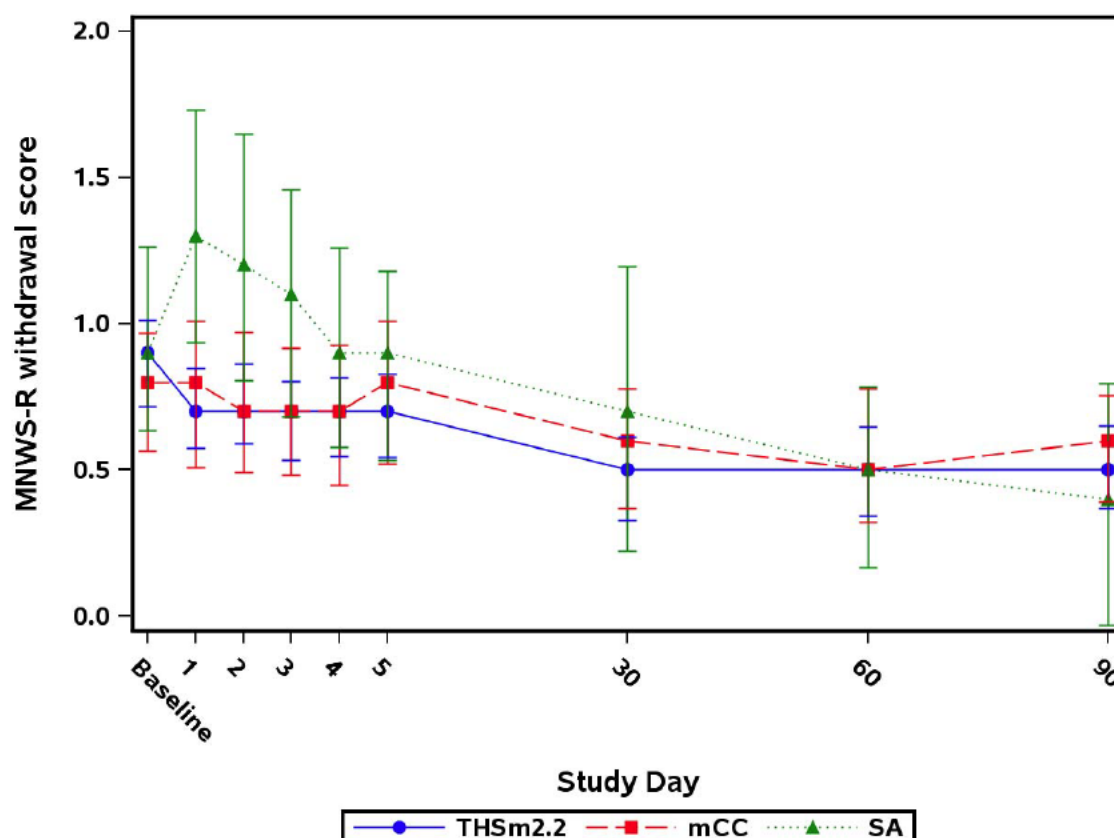
Line graphs showing the arithmetic mean scores and 95% CIs for total score for the MNWS-R questionnaire over the course of the study are presented in [Appendix 15, Figure 15.1.2.8.1](#) and [Figure 15.1.2.8.2](#) for the PP Set and FAS, respectively. Data for the PP Set are also provided in [Figure 60](#).

The MNWS-R version 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-R questionnaire.





**Figure 60 Arithmetic Mean and 95% CI MNWS-R Total Score During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; MNWS-R = Minnesota nicotine withdrawal scale - 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 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 was 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 average MNWS-R withdrawal score values were 0.87 for the THS 2.2 Menthol arm, 0.77 for the mCC arm, and 0.95 for the SA arm at baseline. For the THS 2.2 Menthol and mCC arms, the average MNWS-R withdrawal score values remained comparable to baseline through the Confinement Period (0.67 to 0.73 for the THS 2.2 Menthol arm and 0.69 to 0.76 for the mCC arm; ranges of individual scores were 0.0 to 3.1 for the THS 2.2 Menthol arm and 0.0 to 3.2 for the mCC arm). In the SA arm, the MNWS-R withdrawal score increased from baseline to Day 2 (1.33, corresponding to an increase of 86.72%).



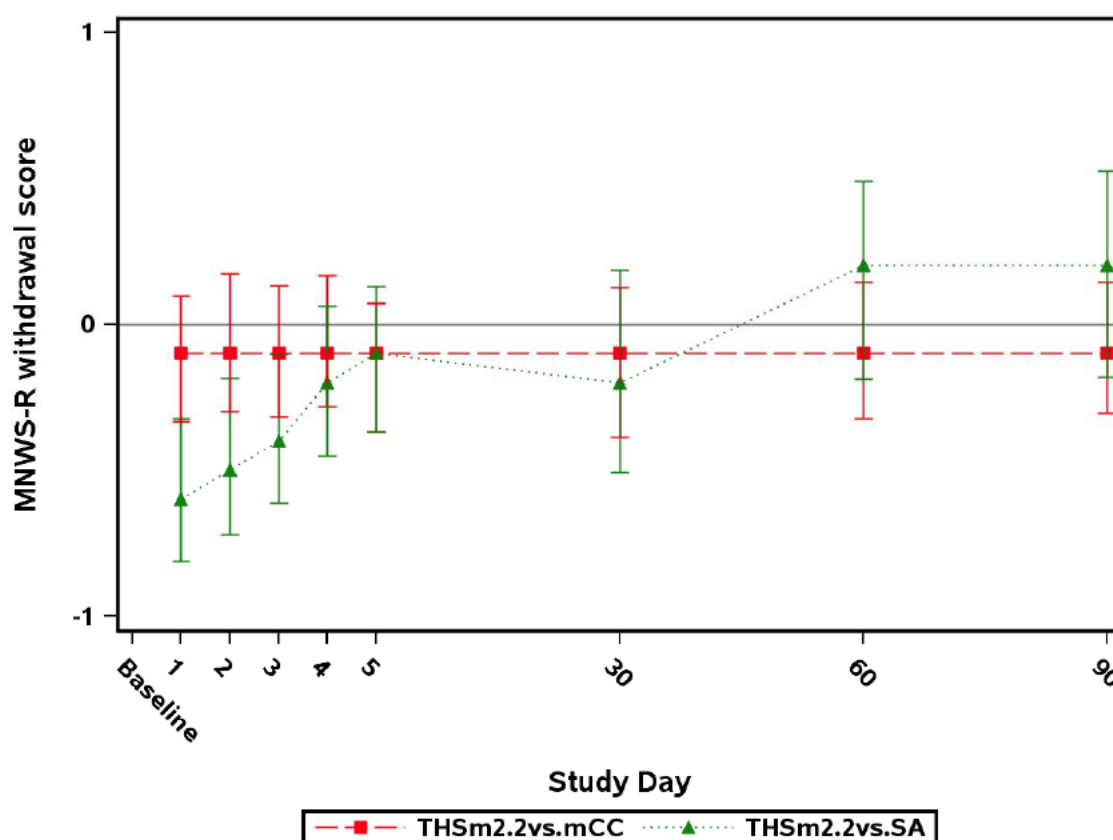
The MNWS-R withdrawal score value then decreased slowly for the remainder of the Confinement Period and was 0.86 at Discharge.

During the Ambulatory Period, the mean MNWS-R withdrawal score values decreased modestly for the THS 2.2 Menthol and mCC arms, with Day 90 values of 0.51 and 0.57, respectively, corresponding to changes from baseline of -16.04% and -16.98%, respectively. In the SA arm, the MNWS-R withdrawal score also decreased from the end of the Confinement Period and was 0.38 on Day 90, which corresponded to a change from baseline of -53.24%.

The results from the statistical analysis of the MNWS-R withdrawal score at Discharge (Day 6) are presented in [Table 120](#) and in [Appendix 15, Table 15.2.4.57.1](#) and [Table 15.2.4.57.2](#) for the PP Set and FAS, respectively. Profiles of the LS mean differences (THS m2.2 – mCC and THS m2.2 – SA) over time are presented in [Appendix 15, Figure 15.1.2.9.1](#) and [Figure 15.1.2.9.2](#) for the PP Set and FAS, respectively, and data for the PP Set are provided in [Figure 61](#).



**Figure 61 Mean and 95% CI Total Scores Least Squares Means Differences for MNWS-R During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; MNWS-R = Minnesota nicotine withdrawal scale – 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 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 -0.12 on Day 2 and -0.15 on Day 6/Discharge Confinement. The LS mean differences of THS 2.2 Menthol – SA for MNWS-R total scores decreased from -0.57 on Day 2 to -0.12 on Day 6/Discharge Confinement ([Figure 61](#)).

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 -0.08 on



Day 90. The LS mean difference of THS 2.2 Menthol – SA for MNWS-R total score on Day 30 (-0.16) was comparable to the difference observed on Day 6/Discharge Confinement. By Day 60 the difference had increased to 0.15 and was 0.17 on Day 90 (Figure 61).

**Table 120 Analysis of MNWS-R Questionnaire Scores on Day 6 (PP Set)**

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – mCC)	
					LS Mean	95% CI
Total score	Day 6	THS m2.2	75	0.67		
		mCC	34	0.82	-0.15	-0.37, 0.08

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Total Score	Day 6	THS m2.2	75	0.67		
		SA	24	0.79	-0.12	-0.37, 0.13

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 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 15.2.4.57.1](#).

At Discharge, there was no notable difference in MNWS-R 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. There was also no notable difference in MNWS-R scores at Discharge between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking with the 95% CI of the LS mean difference spanning 0.

The results for the FAS were consistent with the results for the PP Set.

The results from the statistical analysis of the MNWS-R withdrawal score at the end of the Ambulatory Period (Day 90) are tabulated in [Table 121](#).



**Table 121 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
Total score	Day 90	THS m2.2	47	0.51	-0.08	-0.31, 0.15
		mCC	31	0.59		

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS m2.2 – SA)	
					LS Mean	95% CI
Total score	Day 90	THS m2.2	47	0.51	0.17	-0.19, 0.53
		SA	9	0.34		

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 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 15.2.4.57.1](#).

On Day 90, there was no notable difference in MNWS-R 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. There was also no notable difference in MNWS-R scores on Day 90 between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking with the 95% CI of the LS mean difference spanning 0.

The results for the FAS were consistent with the results for 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 15.3.6.16](#). The subscale scores for the MCEQ are summarized in [Appendix 15, Table 15.2.4.54.1](#) and [Table 15.2.4.54.2](#) for the PP Set and 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 [Figures 15.1.2.6.1](#) and [Figure 15.1.2.6.2](#), respectively.

The profiles of the individual subscale scores showed decreases from baseline in mean score values for most subscales for the THS 2.2 Menthol arm while scores tended to remain comparable to baseline for the mCC arm. In the THS 2.2 Menthol arm, mean



decreases from baseline on Day 1 were evident for craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction, with mean percent decreases from baseline of -22.7%, -16.7%, -22.6%, and -24.4%, respectively. From Day 1 onwards in the Confinement Period the mean scores increased, with percent changes from baseline of -15.0%, 1.3%, -20.8%, and -12.7% for each parameter on Day 5, respectively.

During the Ambulatory Period, mean scores for the individual parameters in the THS 2.2 Menthol arm increased from Day 5 to Day 30, before plateauing thereafter to Day 90 while mean scores in the mCC arm were comparable to baseline throughout the Ambulatory Period. Mean scores on Day 30 in the THS 2.2 Menthol arm were comparable to baseline, and corresponded to percent changes from baseline of 15.3%, 26.0%, -1.2%, and -3.3% for craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, respectively.

The results from the statistical analysis of the MCEQ subscales score are presented in [Appendix 15](#), [Table 15.2.4.55.1](#) and [Table 15.2.4.55.2](#), and [Figure 15.1.2.7.1](#) and [Figure 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 Day 5 are tabulated in [Table 122](#).

**Table 122 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	1.33	0.15	-0.20, 0.49
		mCC	34	1.18		
Craving reduction	Day 5	THS m2.2	75	4.3	-1.1	-1.8, -0.4
		mCC	34	5.4		
Enjoyment of respiratory tract sensation	Day 5	THS m2.2	75	3.9	-0.6	-1.3, 0.1
		mCC	34	4.6		
Psychological reward	Day 5	THS m2.2	75	3.12	-0.40	-0.86, 0.06
		mCC	34	3.52		
Smoking satisfaction	Day 5	THS m2.2	75	4.54	-0.96	-1.50, -0.42
		mCC	34	5.49		

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 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 15.2.4.55.1](#).

On Day 5, 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 and psychological reward subscales, with all 95% CIs of the LS mean difference spanning 0. Craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction were all notably lower for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, although the 95% CI spanned 0 for the enjoyment of respiratory tract sensation subscale.

The results for the FAS were consistent with the results for the PP Set.

The results from the statistical analysis on the PP Set for each MCEQ subscale on Day 90 are presented in [Table 123](#).

**Table 123 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	47	1.22	0.08	-0.18, 0.34
		mCC	31	1.14		
Craving reduction	Day 90	THS m2.2	46	4.6	-0.7	-1.4, 0.0
		mCC	31	5.3		
Enjoyment of respiratory tract sensation	Day 90	THS m2.2	47	4.6	-0.2	-0.8, 0.5
		mCC	31	4.7		
Psychological reward	Day 90	THS m2.2	47	3.47	-0.30	-0.78, 0.17
		mCC	31	3.78		
Smoking satisfaction	Day 90	THS m2.2	47	5.01	-0.37	-0.88, 0.13
		mCC	31	5.39		

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 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 15.2.4.55.1](#).

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, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction MCEQ subscales, with all 95% CIs spanning 0. Craving reduction was still notably lower on Day 90, with an LS mean difference of -0.7 for THS 2.2 Menthol - mCC, although the 95% CI contained 0 (95% CI: -1.4, 0.0).

The results for the FAS were consistent with the results for the PP Set.

### 11.3.5 Oxysterol Assessments During the Study

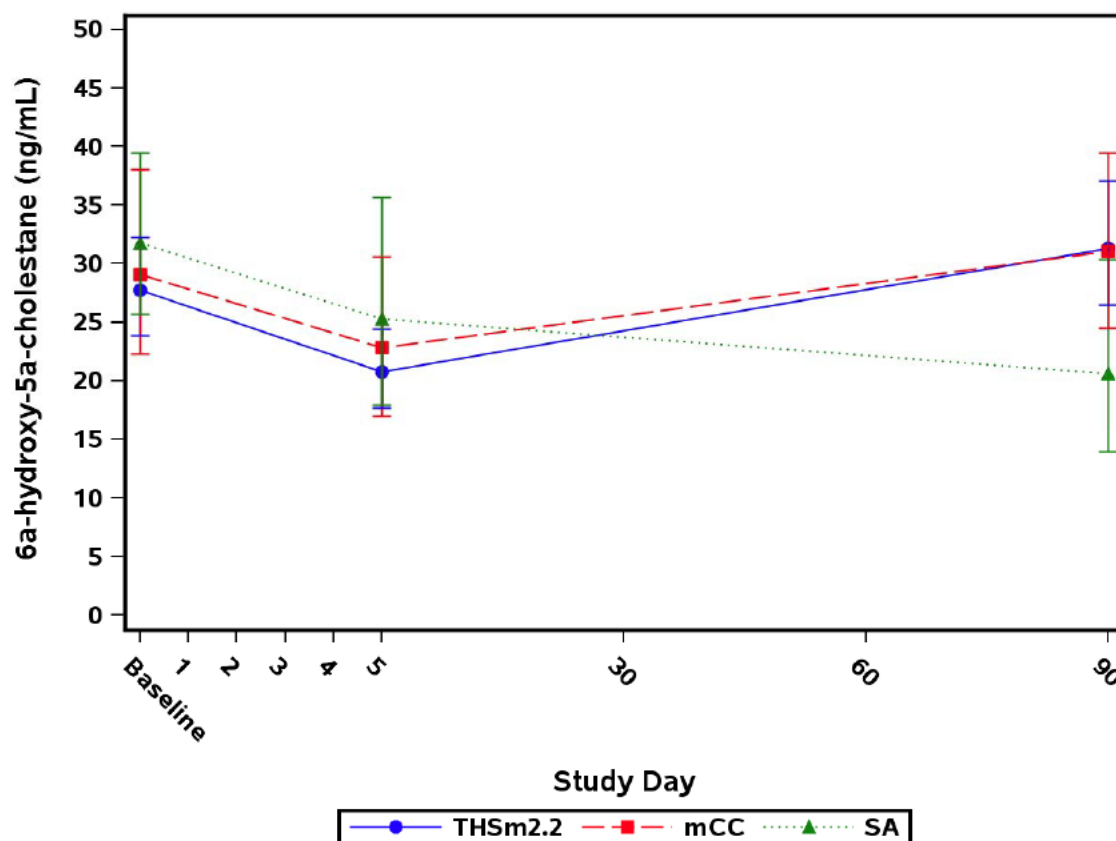
Descriptive statistics of oxysterol parameters during the course of the study are provided together with percent changes from baseline in [Appendix 15, Table 15.2.4.66.1](#) and [Table 15.2.4.66.2](#) for the PP Set and FAS, respectively. Arithmetic mean and 95% CIs for oxysterol parameters are presented graphically in [Appendix 15, Figure 15.1.2.11.1](#) and





Figure 15.1.2.11.2 for the PP Set and FAS, respectively. Data for the PP Set are also presented in Figure 62 to Figure 73.

**Figure 62 Arithmetic Mean and 95% CI 6 $\alpha$ -hydroxy-5 $\alpha$ -cholestane During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

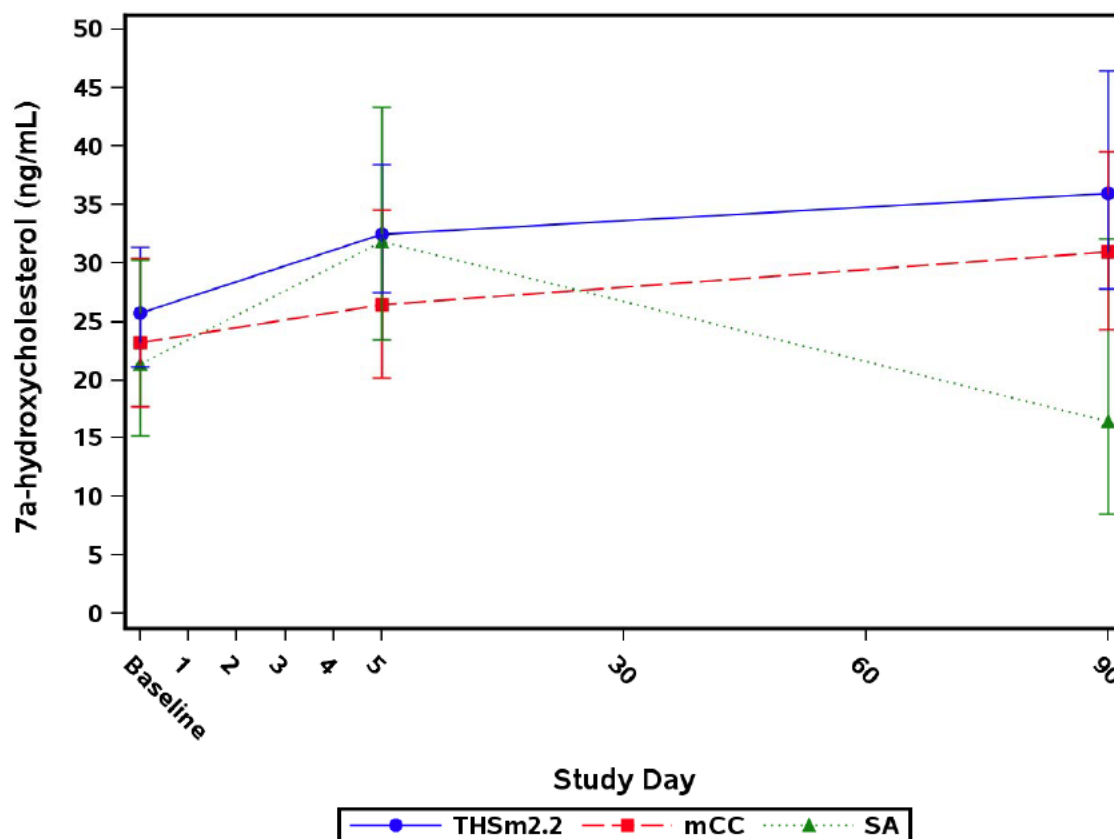
Baseline was defined as the last assessment prior to first product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline was summarized using the baseline data from the PP Set for Period 1.

Data Source: Appendix 15, Figure 15.1.2.11.1.



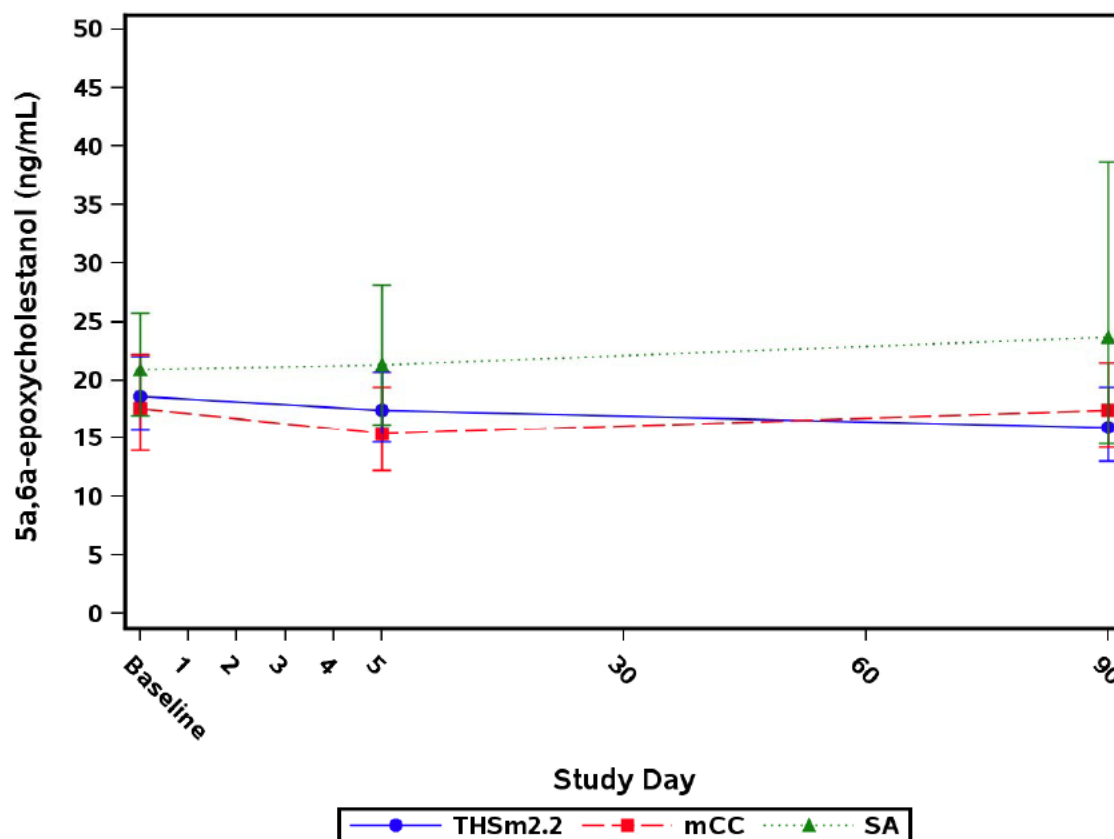
**Figure 63 Arithmetic Mean and 95% CI 7 $\alpha$ -hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



**Figure 64 Arithmetic Mean and 95% CI 5 $\alpha$ ,6 $\alpha$ -epoxycholestanol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

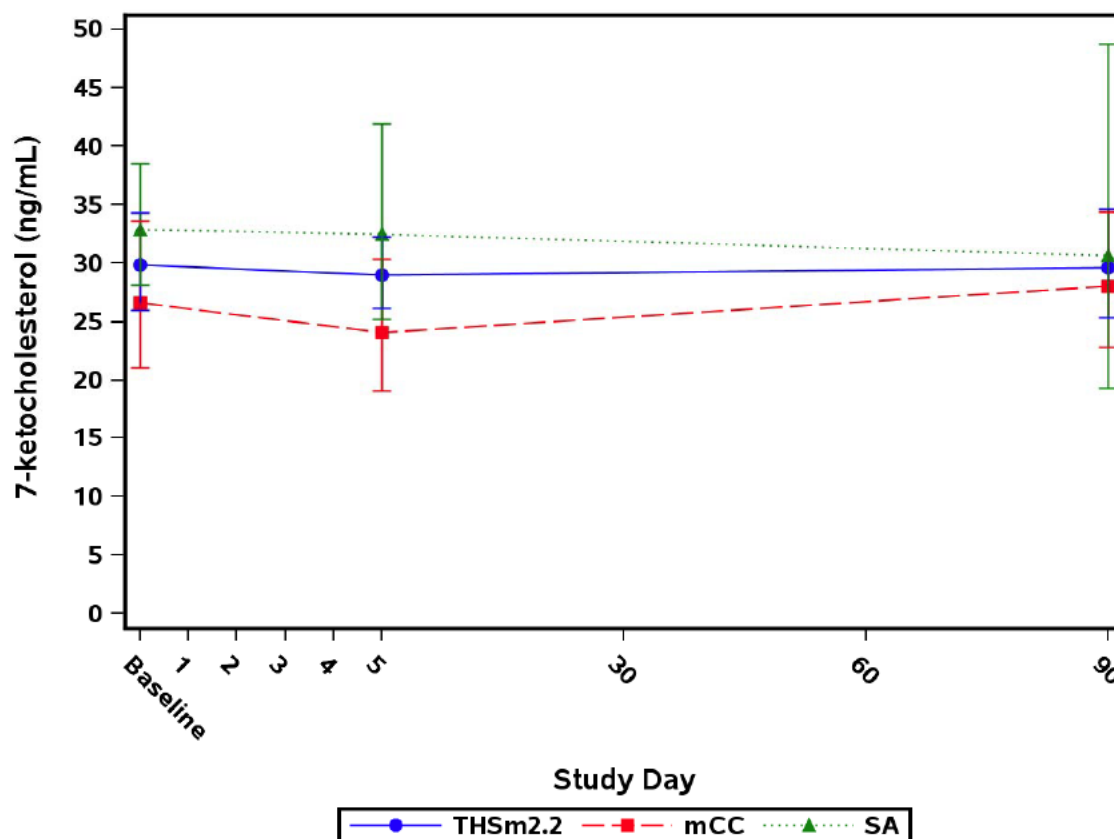
Baseline was defined as the last assessment prior to first product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



**Figure 65 Arithmetic Mean and 95% CI 7-ketocholesterol During the Course of the Study (PP Set)**

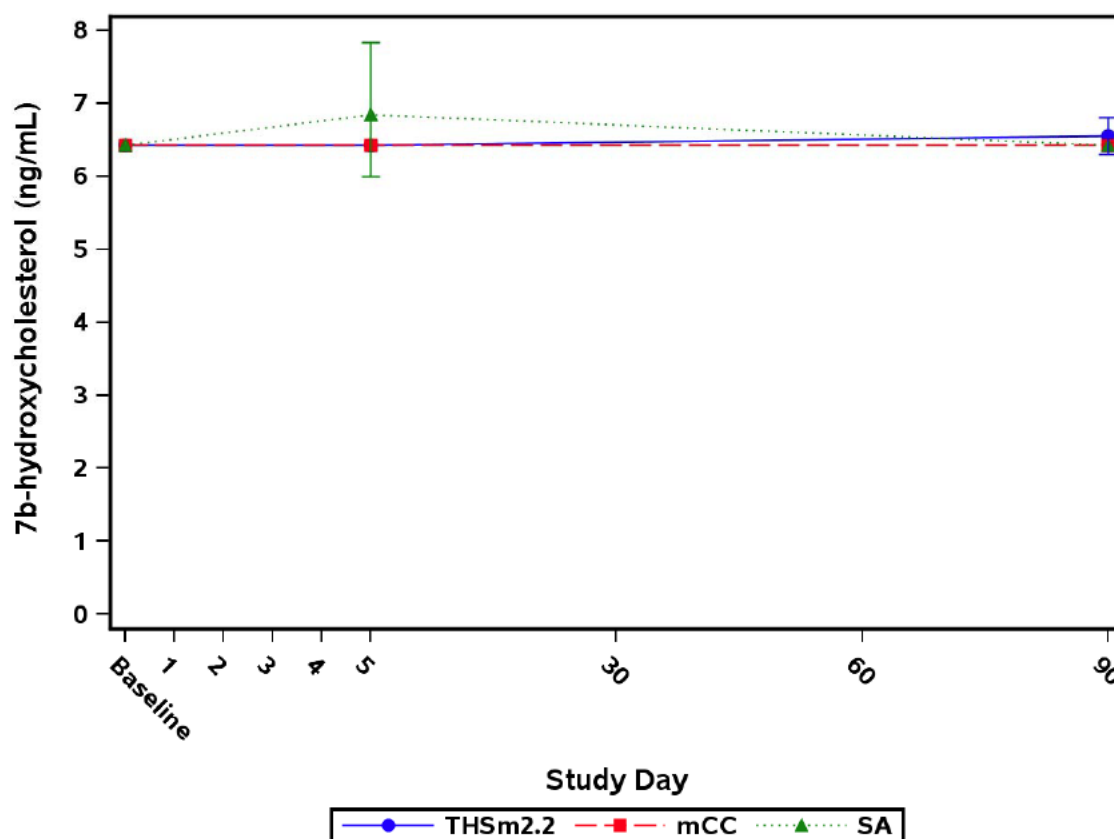


Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Baseline was defined as the last assessment prior to first product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1. Baseline was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).





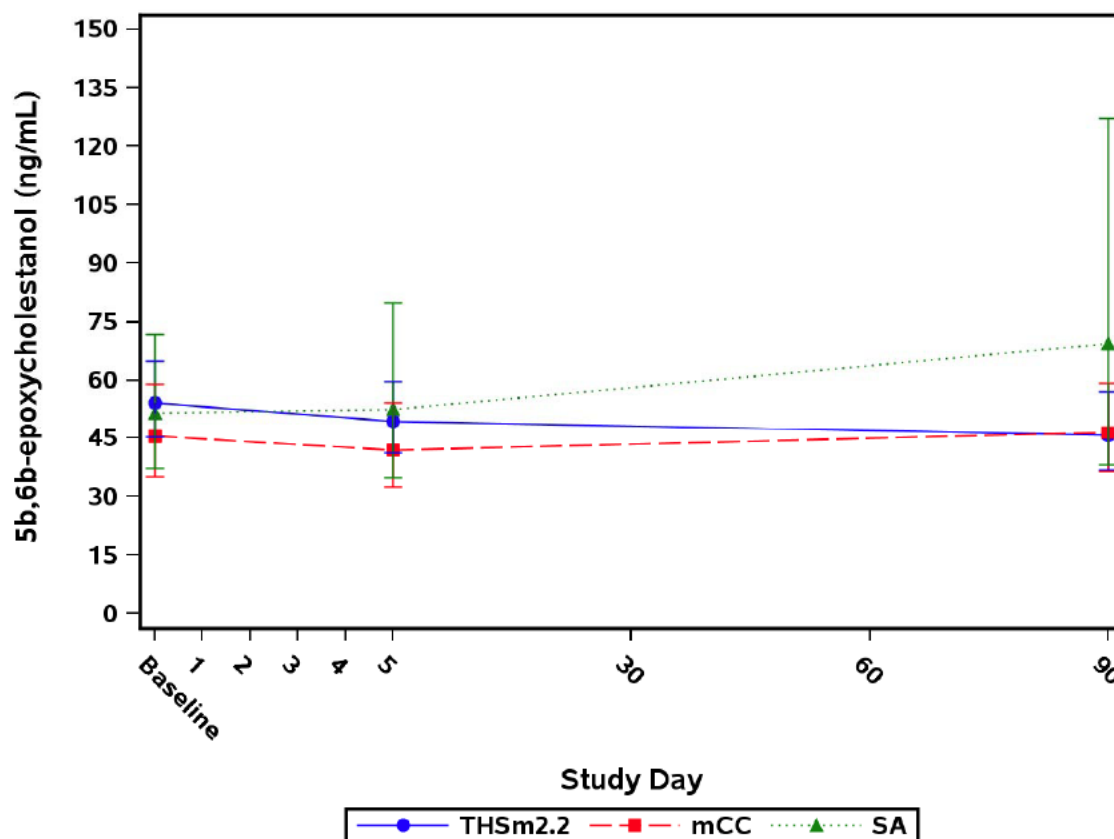
**Figure 66 Arithmetic Mean and 95% CI 7 $\beta$ -hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



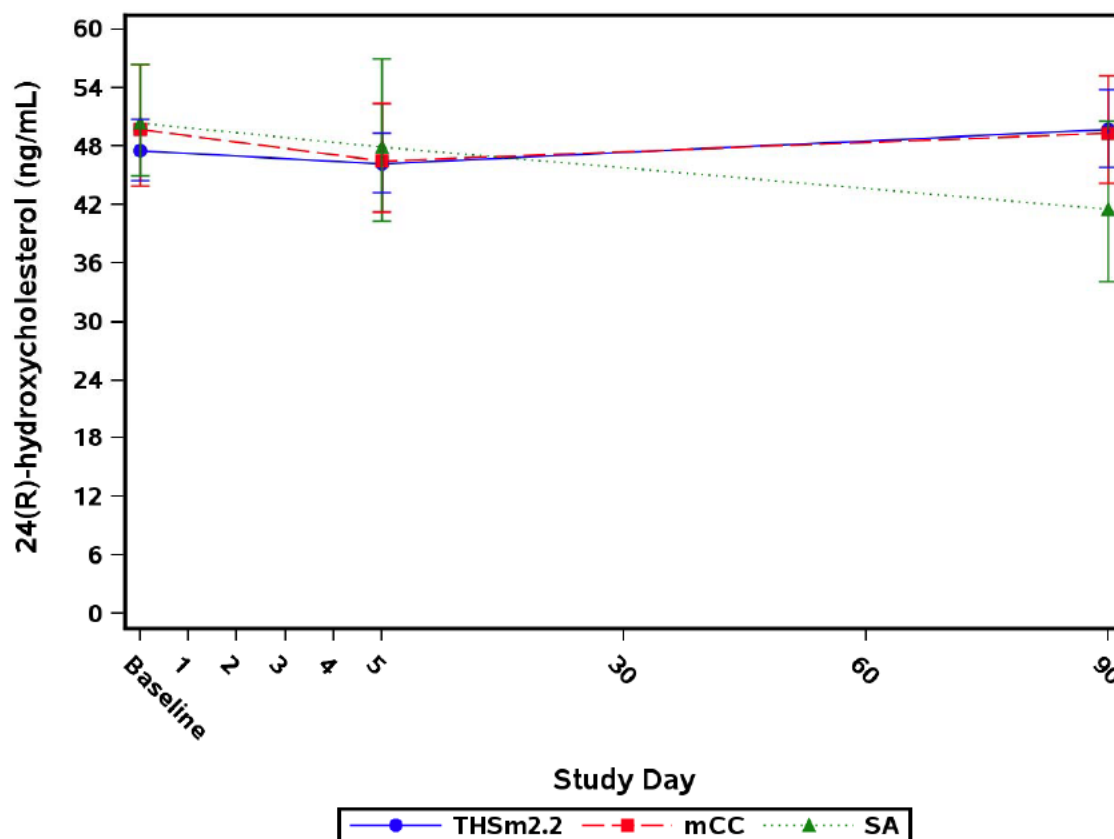
**Figure 67 Arithmetic Mean and 95% CI 5 $\beta$ ,6 $\beta$ -epoxycholestanol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



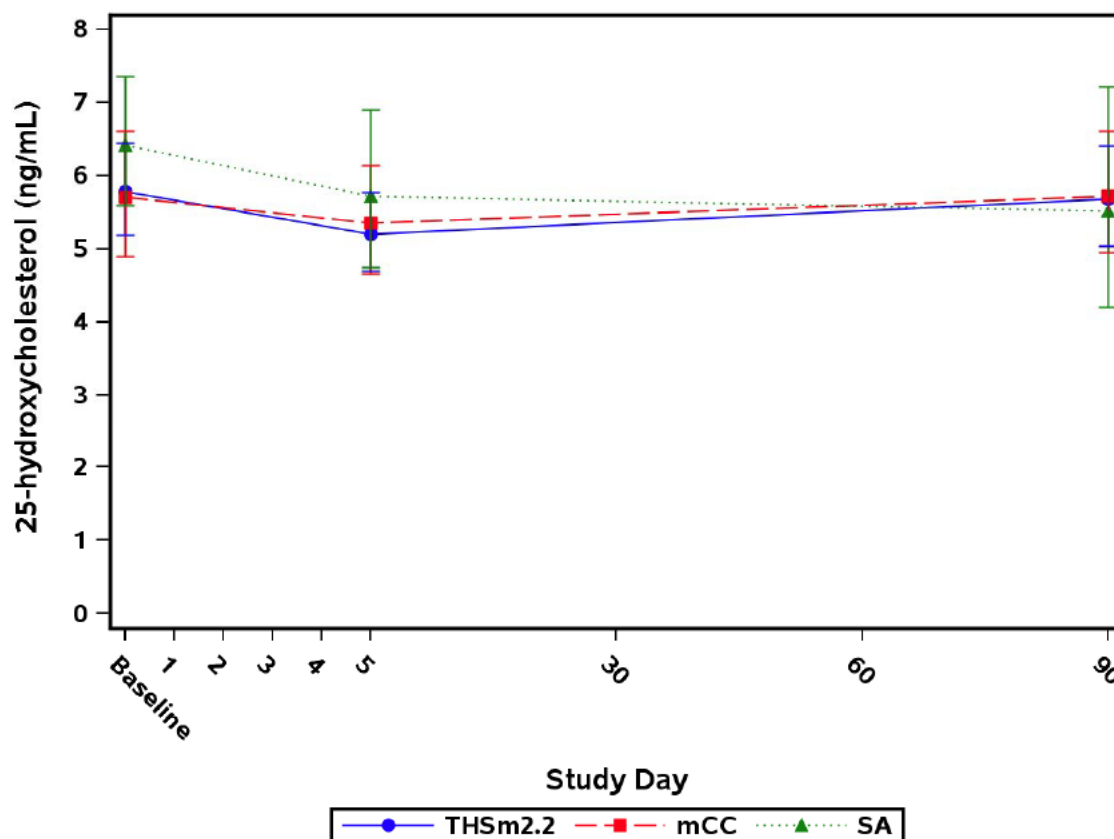
**Figure 68 Arithmetic Mean and 95% CI 24(R)-hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



**Figure 69 Arithmetic Mean and 95% CI 25-hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; mCC = Menthol conventional cigarettes; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

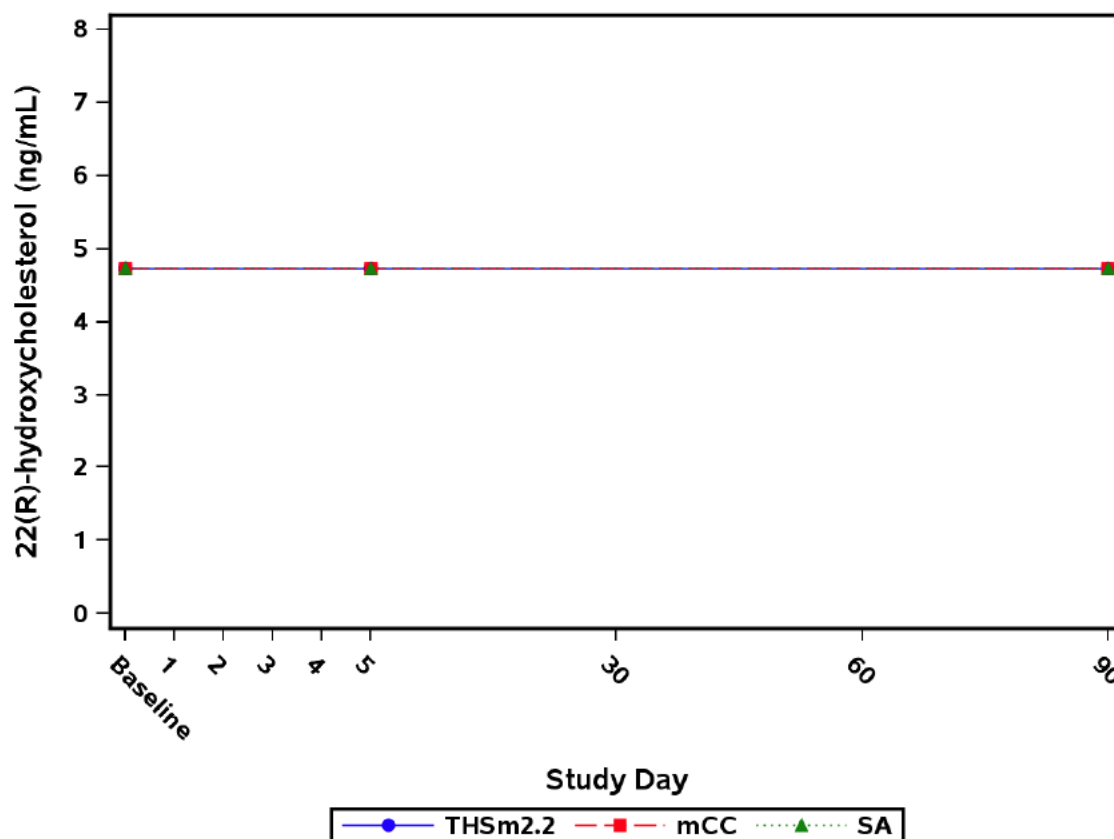
Baseline was defined as the last assessment prior to first product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



**Figure 70 Arithmetic Mean and 95% CI 22(R)-hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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.

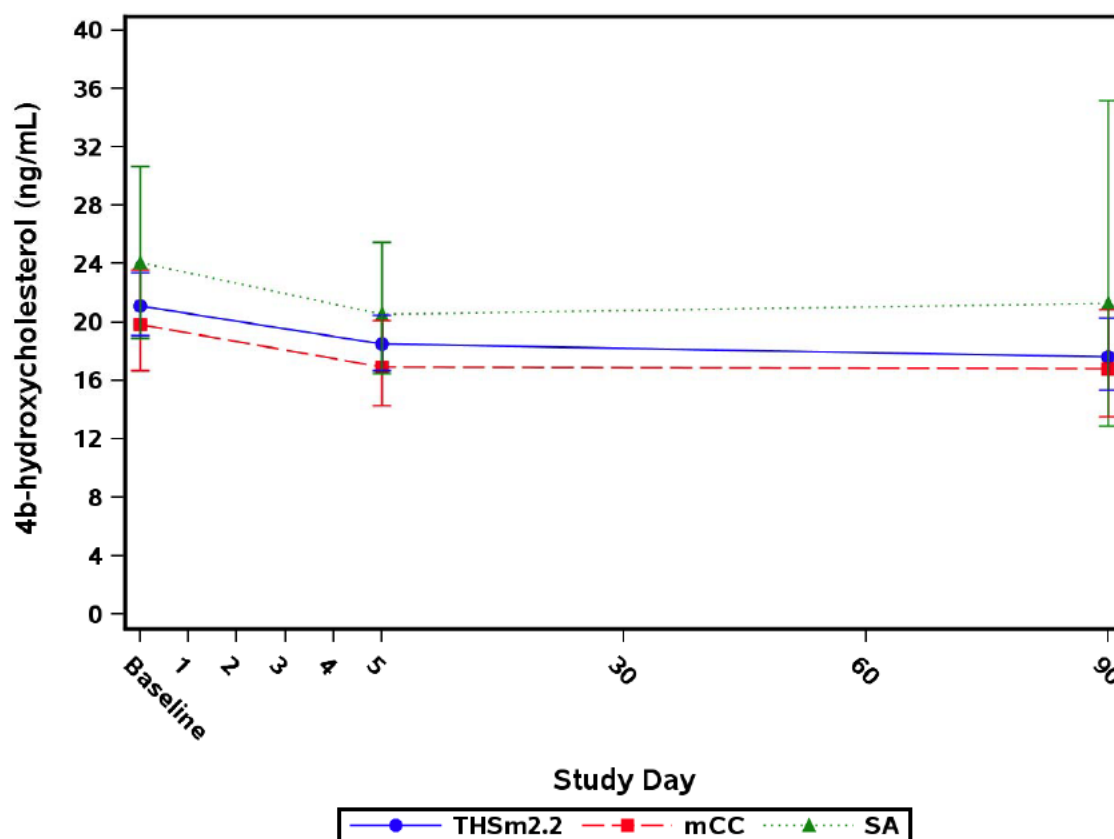
Baseline was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.11.1](#).





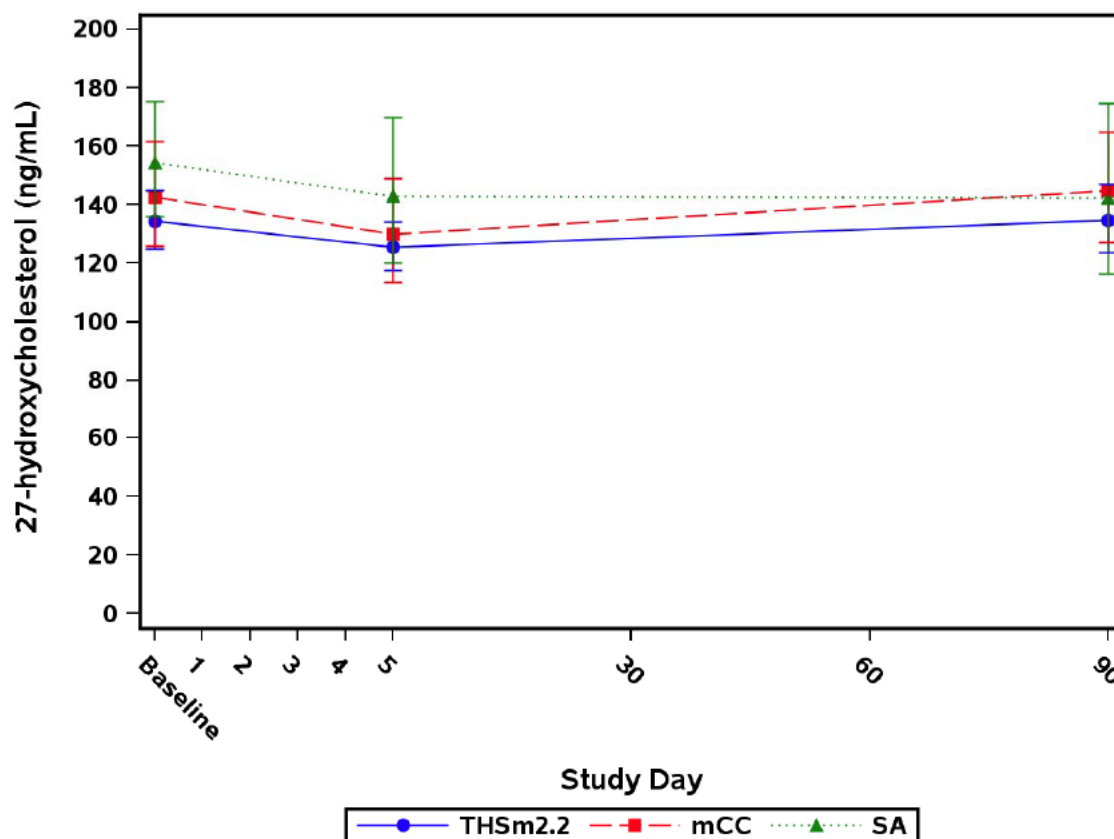
**Figure 71 Arithmetic Mean and 95% CI 4 $\beta$ -hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



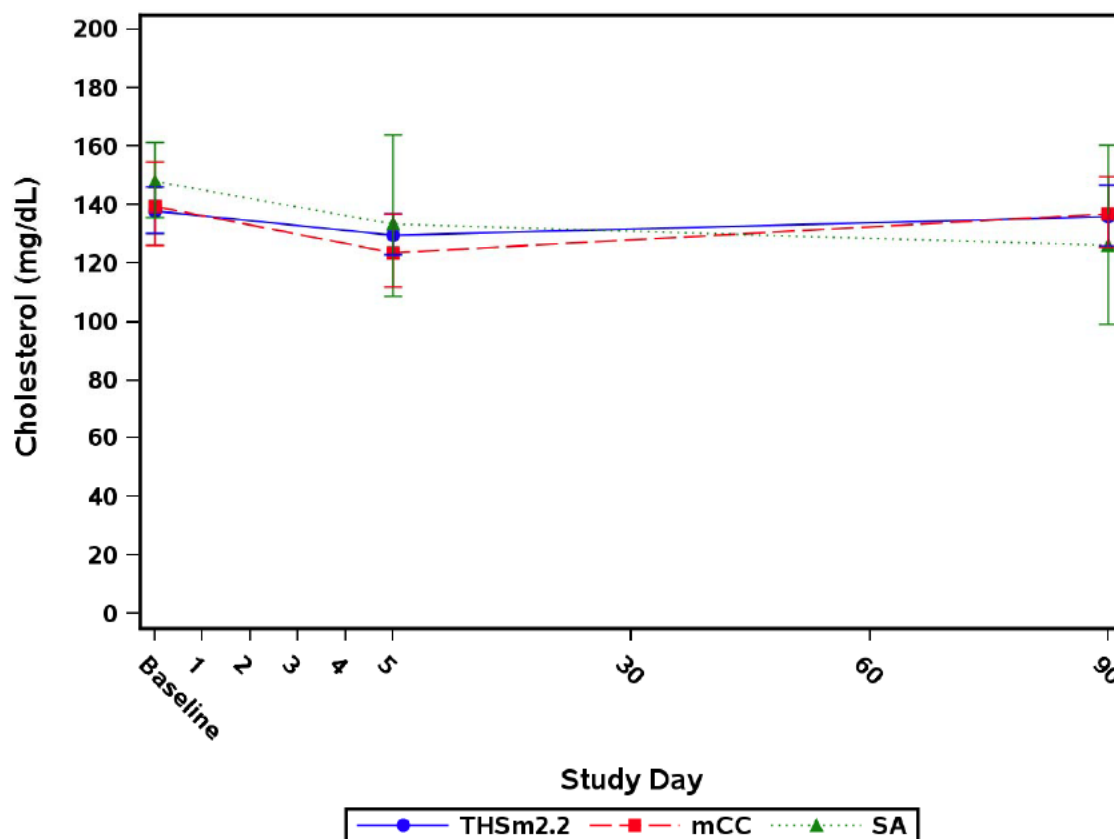
**Figure 72 Arithmetic Mean and 95% CI 27-hydroxycholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1. Data Source: [Appendix 15, Figure 15.1.2.11.1](#).



**Figure 73 Arithmetic Mean and 95% CI Cholesterol During the Course of the Study (PP Set)**



Abbreviations: CI = confidence interval; 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 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 was summarized using the baseline data from the PP Set for Period 1.

Data Source: [Appendix 15, Figure 15.1.2.11.1](#).

For 6 $\alpha$ -hydroxy-5 $\alpha$ -cholestane in the PP Set, levels decreased from baseline to Day 6/Discharge Confinement for all study arms before returning to baseline values on Day 90 in the THS 2.2 Menthol and mCC arms. In the SA arm, levels continued to decrease from Day 6/Discharge Confinement to Day 90; however, this decrease was not observed in the FAS and may be due to the limited number of subjects (N=9) in the PP Set on Day 90.

For 7 $\alpha$ -hydroxycholesterol in the PP Set, levels increased from baseline to Day 6/Discharge Confinement in all study arms and continued to increase on Day 90 in the THS 2.2 Menthol and mCC arms. In the SA arm, levels of 7 $\alpha$ -hydroxycholesterol



decreased from Day 6/Discharge Confinement to Day 90. In the FAS, geometric mean levels of 7 $\alpha$ -hydroxycholesterol decreased from Day 6/Discharge Confinement to Day 90 although the decrease was not as marked as in the PP Set.

For all other oxysterol parameters, the mean values were comparable to baseline on Days 6 and 90 for all study arms.

### 11.3.6 Human Smoking Topography During the Study

#### 11.3.6.1 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 15.2.4.58](#) for the PP Set.

#### 11.3.6.2 Human Smoking Topography

The individual parameters collected from the HST SODIM<sup>®</sup> device and changes from baseline are listed in [Appendix 15, Listing 15.3.7.1](#) and are summarized by product use in [Appendix 15.2.4.60](#) 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 15.2.4.61](#).

[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, total puff volume, average puff volume, total number of puffs, average puff duration, total puff duration, total work, smoking intensity, puffing time index, and puff frequency all increased from baseline to Day 1 and continued to increase on Day 4 for subjects who switched to the THS 2.2 Menthol use compared to subjects who continued to smoke mCC. For the THS 2.2 Menthol, total number of puffs, total work, smoking intensity, puffing time index, and puff frequency remained comparable to the Day 4 value for the Ambulatory Period, whereas total puff volume, average puff volume, average puff duration, and total puff duration decreased from Day 4 to Day 30 and then stabilized for the remainder of the Ambulatory Period.

In contrast, decreases from baseline to Day 4 were observed in the THS 2.2 Menthol arm for average flow, average peak flow, total inter puff interval, average inter puff interval, total smoking duration, average pressure drop, and average peak pressure drop. Average flow and average peak flow remained decreased from baseline for the remainder of the study, while total inter puff interval, average inter puff interval, and total smoking



duration continued to decrease on Day 4 and Day 30 before stabilizing for the remainder of the Ambulatory Period. Average pressure drop and average peak pressure drop remained decreased from baseline on Day 4 and then gradually increased back to baseline values by Day 90.

In the mCC arm, HST parameters remained generally stable during the entire study period, with values similar to those of baseline.

The total number of puffs in the mCC arm was lower compared to THS 2.2 Menthol, with total number of puffs in the THS 2.2 Menthol arm increasing from Day 1, steadily until Day 90; whereas total number of puffs fluctuated around baseline for the mCC arm. In addition, total puff volume and total puff duration were also lower compared to THS 2.2 Menthol, with total puff volume and total puff duration in the THS 2.2 Menthol arm increasing from baseline as of Day 1 and fluctuating around Day 1 values until the EOS. Likewise, puff frequency in mCC was stable throughout, and lower compared to THS 2.2 Menthol. For the THS 2.2 Menthol arm, puff frequency increased sharply from Day 1 until Day 30, whereby it fluctuated until EOS. In contrast, total smoking duration was higher in the mCC arm compared to the THS 2.2 Menthol arm; with values for the THS 2.2 Menthol arm decreasing from baseline from Day 1 and stabilizing at lower levels compared to mCC from Day 4 until the EOS.

Overall, the HST results showed parameters unchanged for mCC; whereas THS 2.2 Menthol puffing pattern changed from the first day after switching to THS 2.2 Menthol, with most parameters reaching a stable, or fluctuating value by Day 4. The most notable differences between the arms were the lower total smoking duration for THS 2.2 Menthol, but higher frequency and total puff volume.

Statistical analysis of the HST parameters on Day 1 and Day 4 is tabulated in [Table 124](#).



**Table 124 Analysis of HST Parameters During the Confinement Period  
(Averaged over All Cigarettes per Day) (PP Set)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC	
					Difference	95% CI
Total number of puffs	Day 1	THS m2.2	47	14.74	1.22	-0.30, 2.75
		mCC	23	13.52		
	Day 4	THS m2.2	46	15.22	1.88	0.45, 3.30
		mCC	21	13.35		
Total puff volume (mL)	Day 1	THS m2.2	47	779.95	126.30	-32.72, 285.31
		mCC	23	653.65		
	Day 4	THS m2.2	46	868.42	187.51	28.11, 346.91
		mCC	21	680.90		
Average puff volume (mL)	Day 1	THS m2.2	47	55.93	7.37	-1.57, 16.31
		mCC	23	48.56		
	Day 4	THS m2.2	46	60.19	8.35	-2.74, 19.44
		mCC	21	51.85		
Average puff duration (s)	Day 1	THS m2.2	47	2.09	0.35	0.09, 0.61
		mCC	23	1.75		
	Day 4	THS m2.2	46	2.19	0.49	0.22, 0.75
		mCC	21	1.70		
Total puff duration (s)	Day 1	THS m2.2	47	30.11	7.88	2.78, 12.98
		mCC	23	22.23		
	Day 4	THS m2.2	46	32.29	11.12	5.55, 16.69
		mCC	21	21.17		



**Table 124 Analysis of HST Parameters During the Confinement Period (Averaged over All Cigarettes per Day) (PP Set) (continued)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC	
					Difference	95% CI
Average flow (mL/s)	Day 1	THS m2.2	47	28.86	-1.98	-5.62, 1.66
		mCC	23	30.84		
	Day 4	THS m2.2	46	30.12	-3.09	-6.72, 0.54
		mCC	21	33.21		
Average peak flow (mL/s)	Day 1	THS m2.2	47	43.55	-2.96	-8.31, 2.38
		mCC	23	46.51		
	Day 4	THS m2.2	46	45.07	-4.74	-10.09, 0.61
		mCC	21	49.80		
Total inter puff interval (s)	Day 1	THS m2.2	47	238.51	-61.17	-90.48, -31.86
		mCC	23	299.68		
	Day 4	THS m2.2	46	225.73	-74.52	-109.87, -39.18
		mCC	21	300.25		
Average inter puff interval (s)	Day 1	THS m2.2	47	17.44	-6.32	-9.29, -3.35
		mCC	23	23.76		
	Day 4	THS m2.2	46	15.62	-8.72	-12.34, -5.11
		mCC	21	24.34		
Total smoking duration (s)	Day 1	THS m2.2	47	267.86	-55.52	-85.03, -26.02
		mCC	23	323.38		
	Day 4	THS m2.2	46	257.38	-65.54	-100.43, -30.65
		mCC	21	322.92		
Total work (mJ)	Day 1	THS m2.2	47	2134.95	176.72	-383.58, 737.01
		mCC	23	1958.23		
	Day 4	THS m2.2	46	2409.04	293.49	-234.17, 821.15
		mCC	21	2115.55		



**Table 124 Analysis of HST Parameters During the Confinement Period (Averaged over All Cigarettes per Day) (PP Set) (continued)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC	
					Difference	95% CI
Average work (mJ)	Day 1	THS m2.2	47	153.31	-1.61	-32.92, 29.70
		mCC	23	154.92		
	Day 4	THS m2.2	46	168.41	0.34	-36.55, 37.23
		mCC	21	168.07		
Average pressure drop (mmWg)	Day 1	THS m2.2	47	226.96	-36.32	-66.83, -5.80
		mCC	23	263.28		
	Day 4	THS m2.2	46	245.91	-32.32	-60.12, -4.52
		mCC	21	278.23		
Average peak pressure drop (mmWg)	Day 1	THS m2.2	47	370.63	-52.04	-100.91, -3.17
		mCC	23	422.67		
	Day 4	THS m2.2	46	398.53	-45.17	-89.93, -0.42
		mCC	21	443.71		
Smoking intensity (mL/s)	Day 1	THS m2.2	47	3.13	1.01	0.29, 1.73
		mCC	23	2.12		
	Day 4	THS m2.2	46	3.63	1.37	0.57, 2.17
		mCC	21	2.26		
Puffing time index (%)	Day 1	THS m2.2	47	11.61	3.80	1.25, 6.36
		mCC	23	7.81		
	Day 4	THS m2.2	46	13.26	5.63	2.57, 8.68
		mCC	21	7.63		
Puff frequency (puffs/min)	Day 1	THS m2.2	47	3.53	0.73	0.20, 1.26
		mCC	23	2.79		
	Day 4	THS m2.2	46	3.89	1.04	0.39, 1.69
		mCC	21	2.84		



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 15.2.4.61](#).

The total puff volume was 126.30 mL (95% CI: -32.72, 285.31) and 187.51 mL (95% CI: 28.11, 346.91) higher on Days 1 and 4, respectively, in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC.

Average flow on Days 1 and 4 was comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC. In contrast, average puff volume and average puff duration were higher on Days 1 and 4 in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, with average puff volume 7.37 mL (95% CI: -1.57, 16.31) and 8.35 mL (95% CI: -2.74, 19.44) higher on Days 1 and 4, respectively and average puff duration 0.35 s (95% CI: 0.09, 0.61) and 0.49 s (95% CI: 0.22, 0.75) higher on Days 1 and 4, respectively.

Subjects who switched to using THS 2.2 Menthol, compared to subjects in the mCC arm, increased the total number of puffs by 1.22 puffs (95% CI: -0.30, 2.75) on Day 1 and by 1.88 puffs (95% CI: 0.45, 3.30) by Day 4. The total smoking duration was approximately 56 s (95% CI: 26.02, 85.03) lower on Day 1 and 66 s (95% CI: 30.65, 100.43) lower on Day 4 for subjects who switched to smoking THS 2.2 Menthol compared to subject who continued to smoke mCC. An increase in puff frequency of 0.73 puffs/min (95% CI: 0.20, 1.26) on Day 1 and 1.04 puffs/min on Day 4 was observed in subjects using THS 2.2 Menthol in comparison with subjects who continued to smoke mCC.

Total puff duration, smoking intensity, and puffing time index were all notably increased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on both Day 1 and Day 4. Total inter puff interval, average inter puff interval, average pressure drop, and average peak pressure drop were all notably decreased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on both Day 1 and Day 4.

No notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC were observed in average peak flow, total work, and average work on both Days 1 and 4, with 95% CIs for each assessment spanning 0.

Statistical analysis of the HST parameters on Day 90 is tabulated in [Table 125](#).

**Table 125 Analysis of HST Parameters During the Ambulatory Period  
(Averaged over All Cigarettes per Day) (PP Set)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	LS Mean	THS m2.2 – mCC	
					Difference	95% CI
Total number of puffs	Day 90	THS m2.2	26	15.73	3.34	-0.13, 6.81
		mCC	13	12.40		
Total puff volume (mL)	Day 90	THS m2.2	26	792.98	169.84	-69.94, 409.61
		mCC	13	623.15		
Average puff volume (mL)	Day 90	THS m2.2	26	51.27	-0.12	-11.29, 11.05
		mCC	13	51.39		
Average puff duration (s)	Day 90	THS m2.2	26	1.98	0.32	-0.08, 0.71
		mCC	13	1.67		
Total puff duration (s)	Day 90	THS m2.2	26	31.92	12.79	2.94, 22.64
		mCC	13	19.13		
Average flow (mL/s)	Day 90	THS m2.2	26	28.08	-7.41	-13.18, -1.65
		mCC	13	35.49		
Average peak flow (mL/s)	Day 90	THS m2.2	26	43.13	-8.93	-17.38, -0.48
		mCC	13	52.05		
Total inter puff interval (s)	Day 90	THS m2.2	26	210.84	-102.87	-161.24, -44.50
		mCC	13	313.71		
Average inter puff interval (s)	Day 90	THS m2.2	26	15.80	-13.27	-21.02, -5.52
		mCC	13	29.07		





**Table 125 Analysis of HST Parameters During the Ambulatory Period  
(Averaged over All Cigarettes per Day) (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	26	243.31	-88.62	-146.88, -30.36
		mCC	13	331.93		
Total work (mJ)	Day 90	THS m2.2	26	2587.96	441.64	-412.42, 1295.70
		mCC	13	2146.32		
Average work (mJ)	Day 90	THS m2.2	26	167.59	-5.81	-51.25, 39.63
		mCC	13	173.40		
Average pressure drop (mmWg)	Day 90	THS m2.2	26	292.79	-2.62	-65.49, 60.26
		mCC	13	295.40		
Average peak pressure drop (mmWg)	Day 90	THS m2.2	26	489.86	25.48	-78.73, 129.68
		mCC	13	464.38		
Smoking intensity (mL/s)	Day 90	THS m2.2	26	3.62	1.46	0.04, 2.87
		mCC	13	2.17		
Puffing time index (%)	Day 90	THS m2.2	26	14.54	8.34	3.22, 13.46
		mCC	13	6.19		
Puff frequency (puffs/min)	Day 90	THS m2.2	26	4.56	2.22	0.55, 3.90
		mCC	13	2.33		

Abbreviations: ANCOVA = analysis of covariance; mCC = Menthol conventional cigarette; CI = confidence interval; HST = human smoking topography; LS = least squares; PP Set = per protocol; 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 15.2.4.61](#).



The total puff volume was 792.98 mL and 623.15 mL respectively in subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (169.84 mL difference; 95% CI: -69.94, 409.61).

Average puff volume and average puff duration was comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with a 0.12 mL (95% CI: -11.29, 11.05) and 0.32 mL (95% CI: -0.08, 0.71) difference, respectively. In contrast, average flow was 7.41 mL/s higher in subjects who continued to smoke mCC (95% CI: 1.65, 13.18).

Subjects using THS 2.2 Menthol, compared to subjects in the mCC arm, increased the total number of puffs (3.34 puffs difference; 95% CI: -0.13, 6.81). The total smoking duration was approximately 1.5 minutes lower for subjects who switched to smoking THS 2.2 Menthol compared to subjects who continued to smoke mCC (-88.62 s difference; 95% CI: -146.88, -30.36) while an increase in puff frequency of 2.22 puffs/min (95% CI: 0.55, 3.90) was observed in subjects using THS 2.2 Menthol in comparison with subjects who continued to smoke mCC.

Total puff duration, smoking intensity, and puffing time index were all notably increased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on Day 90. Average peak flow, total inter puff interval, and average inter puff interval were all notably decreased in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC on Day 90.

No notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC were observed in total work, average work, average pressure drop, and average peak pressure drop at the end of the Ambulatory Period (Day 90), with 95% CIs for each assessment spanning 0.

As per [Section 9.8.2](#), analysis of geometric LS means ratios (THS m2.2:mCC) of the HST parameters was also performed. Geometric means and percentage changes from baseline for the PP Set are summarized by product use in [Appendix 15, Table 15.2.4.42.1](#). Line graphs of geometric mean and 95% CIs are presented for each HST parameter in 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 geometric means for the HST per-cigarette parameters are tabulated in [Appendix 15, Table 15.2.4.43.1](#).

The additional analyses showed that the results for each assessed parameter were generally comparable with the original analyses.



### 11.3.7 Prochaska Questionnaire Results During the Study

Responses to the Prochaska 'Stage of Change' questionnaire results are listed by subject in [Appendix 15, Listing 15.3.6.19](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.59.1](#) and [Table 15.2.4.59.2](#) for the FAS and Compliant Population, respectively.

At baseline in the FAS, all subjects were current smokers and only 1 smoker in the mCC arm was thinking of quitting in the next 30 days. The majority of subjects in the THS 2.2 Menthol, mCC, and SA arms had never tried to quit smoking (80.5%, 82.9%, and 66.7% of subjects, respectively).

On Day 90, all subjects in the THS 2.2 Menthol and mCC arms for the FAS classed themselves as a current smoker (67 and 29 subjects, respectively), while 6 subjects in the SA arm (20.7%) reported they had quit smoking in the last 6 months and 23 subjects (79.3%) classed themselves as current smokers. The majority of subjects in the THS 2.2 Menthol, mCC, and SA arms were not thinking of quitting on Day 90 (77.6%, 82.8%, and 64.0% of subjects, respectively) while 10.4%, 13.8%, and 28.0% of subjects, respectively, were thinking of quitting in the next 30 days, and 11.9%, 3.4%, and 8.0%, respectively, were thinking of quitting in the next 6 months.

### 11.3.8 Visual Inspection of the THS Tobacco Plugs

Results from the inspection of individual tobacco plugs are listed in [Appendix 15, Listing 15.3.6.21](#) and are summarized in [Appendix 15, Table 15.2.4.65](#). Results from the Confinement Period are presented in [Table 126](#).

**Table 126 Summary of Visual Inspection of the THS Tobacco Plug (FAS) During the Confinement Period**

Evaluation	THS m2.2 (N=80)				
	Day 1 n = 976	Day 2 n = 1079	Day 3 n = 1171	Day 4 n = 1144	Day 5 n = 1259
0	940 (99.6)	1030 (99.8%)	1142 (99.1%)	1100 (99.2%)	1217 (98.7%)
1	4 (0.4%)	2 (0.2%)	10 (0.9%)	8 (0.7%)	15 (1.2%)
2	-	-	-	1 (0.1%)	1 (0.1%)
Missing	32	47	19	35	26

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 15.2.4.65](#).

Visual inspection of THS Tobacco Plugs was possible for the majority of plugs on Days 1 to 5, for an average of approximately 1094 plugs per day. On all study days, the majority of THS Tobacco Plugs ( $\geq 98.7\%$  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 0.2% to 1.2%). There were only 2 occurrences among greater than 5600 THS Tobacco Plugs analyzed as reported as showing ashes inside the tobacco plug and burnt paper (grade 2) following visual inspection.

Results from the Ambulatory Period are presented in [Table 127](#).



**Table 127 Summary of Visual Inspection of the THS Tobacco Plug (FAS) During the Ambulatory Period**

Evaluation	THS m2.2 (N=80)		
	Day 30 n = 885	Day 60 n = 794	Day 90 n = 760
0	874 (99.1%)	771 (99.9%)	709 (99.6%)
1	8 (0.9%)	1 (0.1%)	3 (0.4%)
2	-	-	-
Missing	3	22	48

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 15.2.4.65](#).

Visual inspection of THS Tobacco Plugs was possible for the majority of plugs on Days 30, 60, and 90 (>99% each day; approximately 789 plugs per day). On all study days, the majority of THS Tobacco Plugs 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 0.1% to 0.9%).

### 11.3.9 Analysis of Biomarkers of Exposure in 4-hour Urine Fractions

Subject listings of urinary biomarker data in 4-hour urine fractions are provided in [Appendix 15, Listing 15.3.3.5](#).

Descriptive statistics of BoExp concentrations in 4-hour urine fractions at baseline and Day 90 are provided in [Appendix 15, Table 15.2.4.35 to Table 15.2.4.50](#) for the PP Set. Scatter plots showing the correlation of urinary BoExp concentrations adjusted for creatinine from 24-hour urine collections versus 4-hour urine fractions at baseline and Day 90 are presented in [Figure 15.1.2.12.1 to Figure 15.1.2.28.1](#) for the FAS. Bland-Altman plots showing the concordance of urinary BoExp concentrations adjusted for creatinine from 24-hour urine collections with 4-hour urine fraction at baseline and Day 90 are presented in [Figure 15.1.2.12.2 to Figure 15.1.2.28.2](#) for the FAS.

Analyses of BoExp in 4-hour urine fraction versus mCC and SA on Day 90 are presented in [Appendix 15, Table 15.2.4.34 and Table 128](#).



**Table 128 Analysis of Biomarkers of Exposure in 4-hour Fraction versus mCC and SA on Day 90 Visit (PP Set)**

Biomarker	Statistic	THS m2.2	mCC	SA	THS m2.2:mCC Ratio (%)	THS m2.2:SA Ratio (%)
MHBMA – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	121.30	793.12	152.21	15.29 (94.67)	79.69 (94.67)
	95% CI	95.62, 153.87	596.62, 1054.32	88.66, 261.30	10.55, 22.17	44.30, 143.35
3-HPMA – 4H (ng/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	196.36	508.17	126.66	38.64 (55.64)	155.03 (55.64)
	95% CI	168.26, 229.17	422.54, 611.15	89.11, 180.04	30.38, 49.14	105.73, 227.30
S-PMA – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	173.40	1313.70	121.19	13.20 (111.60)	143.08 (111.60)
	95% CI	132.61, 226.72	954.29, 1808.46	66.01, 222.49	8.70, 20.03	74.06, 276.40
Total NNAL – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	43.98	163.85	32.86	26.84 (107.09)	133.86 (107.09)
	95% CI	33.93, 57.00	120.10, 223.53	18.21, 59.29	17.92, 40.20	70.58, 253.87
Total 1-OHP – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	81.86	136.95	74.19	59.78 (40.79)	110.35 (40.79)
	95% CI	72.69, 92.20	119.10, 157.46	56.76, 96.96	49.73, 71.85	82.21, 148.11

**Table 128 Analysis of Biomarkers of Exposure in 4-hour Fraction versus mCC and SA on Day 90 Visit (PP Set)**

Biomarker	Statistic	THS m2.2	mCC	SA	THS m2.2:mCC Ratio (%)	THS m2.2:SA Ratio (%)
Total NNN – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	0.77	4.42	0.19	17.54 (101.69)	412.96 (101.69)
	95% CI	0.60, 1.00	3.27, 5.96	0.10, 0.34	11.89, 25.86	221.82, 768.80
4-ABP – 4H (pg/mg creat)	n	46	32	9		
	Geometric LS mean (CV%)	3.16	12.76	2.49	24.75 (95.26)	126.88 (95.26)
	95% CI	2.48, 4.03	9.59, 16.99	1.44, 4.29	17.04, 35.95	70.29, 229.01
1-NA – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	5.15	66.86	4.10	7.71 (85.60)	125.64 (85.60)
	95% CI	4.13, 6.42	51.36, 87.05	2.48, 6.77	5.47, 10.85	72.95, 216.35
2-NA – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	2.76	17.10	2.99	16.12 (74.96)	92.32 (74.96)
	95% CI	2.26, 3.36	13.48, 21.68	1.90, 4.69	11.84, 21.94	56.58, 150.64
o-tol – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	50.17	108.82	51.85	46.10 (65.63)	96.75 (65.63)
	95% CI	41.99, 59.92	87.95, 134.64	34.61, 77.67	34.98, 60.75	62.40, 149.99

**Table 128 Analysis of Biomarkers of Exposure in 4-hour Fraction versus mCC and SA on Day 90 Visit (PP Set)**

<b>Biomarker</b>	<b>Statistic</b>	<b>THS m2.2</b>	<b>mCC</b>	<b>SA</b>	<b>THS m2.2:mCC Ratio (%)</b>	<b>THS m2.2:SA Ratio (%)</b>
CEMA – 4H (ng/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	9.88	77.09	10.43	12.81 (99.56)	94.65 (99.56)
	95% CI	7.72, 12.63	57.40, 103.52	5.95, 18.28	8.73, 18.79	51.56, 173.76
HEMA – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	1093.15	2501.18	1057.69	43.71 (57.30)	103.35 (57.30)
	95% CI	933.75, 1279.77	2069.41, 3023.04	737.20, 1517.52	34.18, 55.87	69.92, 152.77
B[a]P – 4H (fg/mg creat)	n	46	32	9		
	Geometric LS mean (CV%)	47.45	97.27	40.32	48.78 (76.83)	117.69 (76.83)
	95% CI	38.45, 58.55	76.28, 124.03	25.35, 64.10	35.29, 67.43	70.63, 196.10
HMPMA – 4H (ng/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	68.89	241.18	82.71	28.56 (80.31)	83.30 (80.31)
	95% CI	55.83, 85.00	187.61, 310.04	51.34, 133.21	20.58, 39.65	49.61, 139.86
S-BMA – 4H (pg/mg creat)	n	47	32	9		
	Geometric LS mean (CV%)	3464.77	2941.21	3593.26	117.80 (82.55)	96.42 (82.55)
	95% CI	2796.60, 4292.59	2276.45, 3800.09	2203.02, 5860.80	84.39, 164.44	56.85, 163.55

**Table 128 Analysis of Biomarkers of Exposure in 4-hour Fraction versus mCC and SA on Day 90 Visit (PP Set)**

Biomarker	Statistic	THS m2.2	mCC	SA	THS m2.2:mCC Ratio (%)	THS m2.2:SA Ratio (%)
NEQ – 4H	n	47	31	9		
(mg/mg creat)	Geometric LS mean (CV%)	6.61	7.30	0.63	90.57 (78.68)	1046.31 (78.68)
	95% CI	5.38, 8.12	5.67, 9.40	0.39, 1.01	65.57, 125.09	629.49, 1739.12

Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 3-HPMA = 3-hydroxypropylmercapturic acid; 4-ABP = 4-aminobiphenyl; ANCOVA = analysis of covariance; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CV = coefficient of variation; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = Menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NEQ = nicotine equivalents; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; 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.

Adjusted geometric LS means and CIs from an ANCOVA model conducted with log-transformed baseline values, sex, average daily mCC consumption, and randomized arm as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Data Source: [Appendix 15, Table 15.2.4.34](#).



On Day 90, reductions in each of the BoExp assessed (except S-BMA and NEQ) of approximately 40% to 92% were observed from analysis of 4-hour urine fractions of subjects who switched to THS 2.2 Menthol compared to those of subjects who maintained their mCC use. This range compares well with the reductions in each of the BoExp assessed of 34% to 86% obtained from the full 24-hour urine collections on Day 90 (Sections 11.2.1 and 11.2.3). For the most part, the reductions observed in the 4-hour fraction were similar to those of the 24-hour collection, with the largest differences between the 2 methods observed with 3-HPMA (48% reduction from the 24-hour collection compared with a 61% reduction from the 4-hour fraction) and HMPMA (50% reduction from the 24-hour collection compared with a 71% reduction from the 4-hour fraction).

From analysis of the 4-hour fractions, there were no notable differences (based on 95% CIs) on Day 90 between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking for most BoExp. The exceptions were 3-HPMA and Total NNN which were 55% and 4.1-fold higher, respectively, in subjects who switched to THS 2.2 Menthol compared with subjects who abstained from smoking. These results are consistent with the results from the 24-hour collections on Day 90 where the only notable differences were observed in 3-HPMA and Total NNN (47% and 2.7-fold higher, respectively).

The scatter plots (Appendix 15, Figure 15.1.2.12.1 to Figure 15.1.2.28.1) showed good correlation between BoExp concentrations adjusted for creatinine from 24-hour urine collection and the 4-hour urine fractions at baseline and Day 90. For all BoExp assessed, the Spearman Rank correlation coefficient ( $\rho$ ) value was between 0.6538 and 0.9257. A  $\rho$  value  $>0.7$  represents good correlation, and all values were  $>0.7$  except for HMPMA.

The Bland-Altman plots (Appendix 15, Figure 15.1.2.12.2 to Figure 15.1.2.28.2) also showed good concordance between the results of the 24-hour collections and the 4-hour fractions, with geometric mean 24-hour: 4-hour ratios varying between 84.85% and 137.53%.

## 11.4 Statistical and Analytical Issues

### 11.4.1 Sample Size

It was planned that a total of 160 smokers would be randomized, to demonstrate a reduction of at least 50% on all 5 primary BoExp analysis 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 (see Section 9.7.5 for details relating to the determination of the sample size).





#### 11.4.2 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.

#### 11.4.3 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, values lower than the limit of quantification (LLOQ) 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 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 last observation carried forwards 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 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 Period 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 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-R, QSU-brief, and MCEQ questionnaire data, total scores and domain 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, see the SAP ([Appendix 16.1.8](#)) for more details.

#### 11.4.4 Interim Analysis and Data Analysis

No interim analysis was planned or conducted for this study.

#### 11.4.5 Multicenter Studies

This was a two-site 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 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

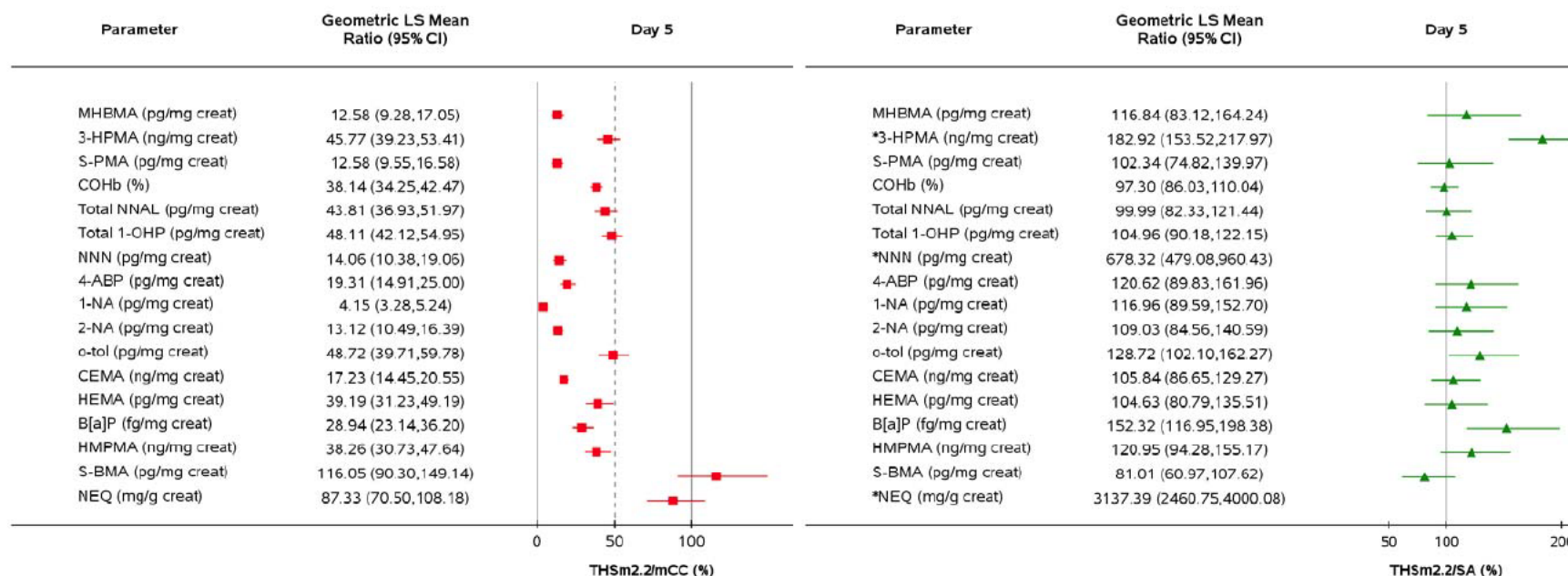
Results for the exploratory sub-groups are discussed in the appropriate sections along with the main analyses.



## 11.5 Conclusions

### 11.5.1 Summary of Statistical Analysis During the Study

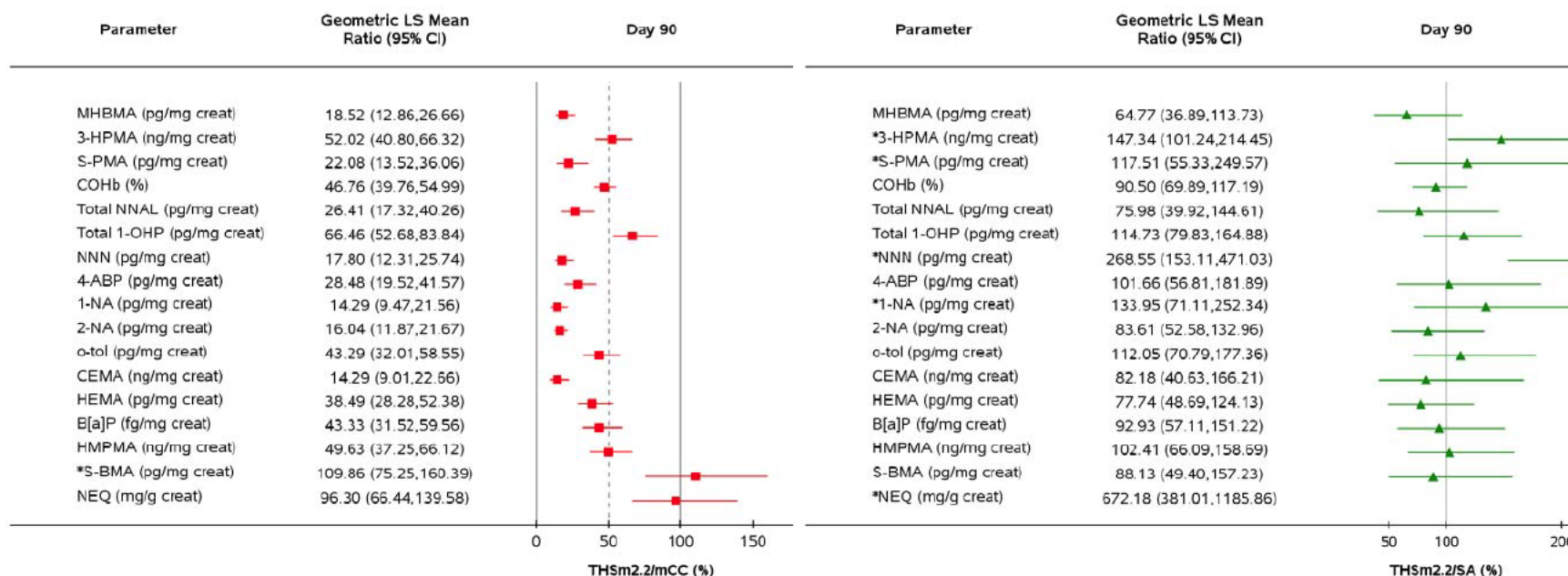
A graphical summary of statistical analysis for all BoExp adjusted for creatinine for the THS 2.2 Menthol arm versus mCC or SA on Day 5 during the Confinement Period and on Day 90 following the Ambulatory Period is presented graphically in [Figure 74](#) and [Figure 75](#), respectively.

**Figure 74 Forest Plot of Statistical Analysis of Biomarkers 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; LS = least squares; mCC = Menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NEQ = nicotine equivalents; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; NNN = N-nitrosornornicotine; 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.

\* The estimate or CI is outside of the reporting scale.

Data Source: Appendix 15, Figure 15.1.1.1

**Figure 75 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; LS = least squares; mCC = Menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NEQ = nicotine equivalents; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; 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.

\* The estimate or CI is outside of the reporting scale.

Data Source: Appendix 15, Figure 15.1.1.1.





## 11.5.2 Conclusions of the Study

### Primary Objectives and Endpoint Analyses

The primary objectives for this study were assessed on Day 5 for the BoExp COHb (expressed as % saturation of hemoglobin); and for the following urinary BoExp expressed as urinary concentration adjusted for creatinine: MHBMA (pg/mg creat); 3-HPMA (ng/mg creat); and S-PMA (pg/mg creat); and on Day 90 for urinary Total NNAL expressed as urinary concentration adjusted for creatinine (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 62% (95% CI: 57.5, 65.8) in COHb, 87% (95% CI: 83.0, 90.7) in MHBMA, 54% (95% CI: 46.6, 60.8) in 3-HPMA, and 87% (95% CI: 83.4, 90.5) in S-PMA. In addition, on Day 90, a reduction of 74% (95% CI: 59.7, 82.7) 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 greater than 50% reduction in smokers that switched to THS 2.2 Menthol compared to smokers that continued to smoke mCC.

**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)*

<b>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)</b>				
<b>Biomarker/ Time point</b>	<b>Geometric LS Mean Ratio (THS m2.2:mCC)</b>		<b>Geometric LS Mean Ratio (THS m2.2:SA)</b>	
	<b>(%)</b>	<b>95% CI</b>	<b>(%)</b>	<b>95% CI</b>
Evening COHb (%)				
Day 5	38.14	34.24, 42.47	97.30	86.02, 110.05
Day 90	46.76	39.75, 55.00	90.50	69.88, 117.19
Urinary MHBMA (pg/mg creat)				
Day 5	12.58	9.27, 17.05	116.84	83.12, 164.24
Day 90	18.52	12.85, 26.67	64.77	36.88, 113.74
Urinary 3-HPMA (ng/mg creat)				
Day 5	45.77	39.22, 53.41	182.92	153.51, 217.97
Day 90	52.02	40.80, 66.33	147.34	101.23, 214.45
Urinary S-PMA (pg/mg creat)				
Day 5	12.58	9.54, 16.58	102.34	74.82, 139.37
Day 90	22.08	13.52, 36.06	117.51	55.32, 249.57
Urinary Total NNAL (pg/mg creat)				
Day 5	43.81	36.92, 51.97	99.99	82.32, 121.44
Day 90	26.41	17.31, 40.26	75.98	39.92, 144.61

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; ANCOVA = analysis of covariance; CI = confidence interval; COHb = carboxyhemoglobin; 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.

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 maintained during the Ambulatory Period, with decreases of 53% in COHb, 81% in MHBMA, 48% in 3-HPMA, and 78% in S-PMA, evident on Day 90. In addition, the initial reductions in the levels of Total NNAL observed on Day 5 (56%) further decreased until Day 90 (74%) 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, S-PMA, and Total NNAL.



The level of 3-HPMA was 83% higher on Day 5 and 47% higher on Day 90 for the THS 2.2 Menthol arm compared to the SA arm. 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.

*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*

<b>Analysis of Other Biomarkers of Exposure on Day 5 and on Day 90 versus mCC and versus SA (PP Set)</b>				
<b>Biomarker/ Time point</b>	<b>Geometric LS Mean Ratio (THS m2.2:mCC)</b>		<b>Geometric LS Mean Ratio (THS m2.2:SA)</b>	
	<b>(%)</b>	<b>95% CI</b>	<b>(%)</b>	<b>95% CI</b>
Urinary Total 1-OHP (pg/mg creat)				
Day 5	48.11	42.11, 54.96	104.96	90.17, 122.16
Day 90	66.46	52.67, 83.84	114.73	79.83, 164.88
Urinary Total NNN (pg/mg creat)				
Day 5	14.06	10.38, 19.06	678.32	479.07, 960.44
Day 90	17.80	12.31, 25.75	268.55	153.11, 471.04
Urinary 4-ABP (pg/mg creat)				
Day 5	19.31	14.90, 25.01	120.62	89.83, 161.97
Day 90	28.48	19.51, 41.58	101.66	56.81, 181.90
Urinary 1-NA (pg/mg creat)				
Day 5	4.15	3.28, 5.25	116.96	89.59, 152.70
Day 90	14.29	9.47, 21.56	133.95	71.10, 252.34
Urinary 2-NA (pg/mg creat)				
Day 5	13.12	10.49, 16.40	109.03	84.55, 140.59
Day 90	16.04	11.87, 21.67	83.61	52.57, 132.97
Urinary o-toluidine (pg/mg creat)				
Day 5	48.72	39.70, 59.79	128.72	102.10, 162.28
Day 90	43.29	32.00, 58.55	112.05	70.79, 177.37
Urinary CEMA (ng/mg creat)				
Day 5	17.23	14.44, 20.55	105.84	86.65, 129.27
Day 90	14.29	9.01, 22.67	82.18	40.63, 166.22
Urinary HEMA (pg/mg creat)				
Day 5	39.19	31.22, 49.20	104.63	80.79, 135.51
Day 90	38.49	28.28, 52.38	77.74	48.68, 124.14



Urinary B[a]P (fg/mg creat)				
Day 5	28.94	23.14, 36.20	152.32	116.94, 198.39
Day 90	43.33	31.52, 59.57	92.93	57.11, 151.22
Urinary HMPMA (ng/mg creat)				
Day 5	38.26	30.73, 47.64	120.95	94.28, 155.18
Day 90	49.63	37.25, 66.13	102.41	66.08, 158.69
Urinary S-BMA (pg/mg creat)				
Day 5	116.05	90.29, 149.14	81.01	60.97, 107.63
Day 90	109.86	75.25, 160.39	88.13	49.39, 157.24

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; 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 -19.96 (-21.62, -18.31) versus mCC and 0.17 (-1.72, 2.07) versus SA; Day 90 -14.62 (-17.67, -11.57) versus mCC and -0.10 (-4.99, 4.78) versus SA.

Reductions observed in the THS 2.2 Menthol arm compared to the mCC arm (excluding S-BMA) ranged from 34% (Total 1-OHP) to 96% (1-NA) on Days 5 and 90.

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 6.8-fold and 2.7-fold higher in the THS 2.2 Menthol arm compared to the SA arm on Day 5 and Day 90, respectively. However, the numerical values for both the THS and SA arms were very low, i.e., within the range of 0.91 and 0.13 pg/mg creat respectively, and the majority of the decrease of the SA arms was preserved in THS 2.2 Menthol arm.

Levels of S-BMA on Day 90 were comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued smoking mCC or 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 from baseline to Day 2 (-21.27%) and then increased from Day 3 to Day 5 up to Day 30 (6.60%), with NEQ levels similar to baseline on Days 60 and 90 (-1.39% and -3.86%, respectively).

On Day 5, NEQ urinary concentration adjusted for creatinine was 13% lower in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC (95% CI: -8.2, 29.5). 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 (96%; 95% CI: 66.4, 139.6).

A similar trend was observed for nicotine and cotinine concentrations in plasma. On Day 5, the levels of nicotine and cotinine at between 08:00 and 09:30 PM were 20% and 16% lower, respectively, in the THS 2.2 Menthol arm compared to the mCC arm (95% CI: 3.4, 34.3 for nicotine; and 95% CI: 1.8, 28.0 for cotinine). These differences decreased over time, starting from Day 30. On Days 30, 60, and 90, plasma nicotine concentrations were approximately 8%, 14%, and 28% lower in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, although the 95% CIs spanned 100%. On Days 30, 60, and 90, plasma cotinine concentrations were approximately 13%, 6%, and 3% higher in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC, although the 95% CIs spanned 100%.

For the nicotine PK profile on Day 5,  $C_{peak}$  and weighted average concentrations were 11% (95% CI: -8.5, 26.3; 20.96 ng/mL for THS 2.2 Menthol arm and 23.43 ng/mL for the mCC arm) lower and 15% (95% CI: -5.6, 31.3; 11.05 ng/mL for THS 2.2 Menthol arm and 12.97 ng/mL for the mCC arm) lower, respectively in the THS 2.2 Menthol arm compared to the mCC arm. For cotinine PK profile on Day 5, peak and weighted average plasma concentrations were 15% (95% CI: -2.7, 29.1; 217.64 ng/mL for THS 2.2 Menthol arm and 254.96 ng/mL for the mCC arm) and 18% (95% CI: -0.9, 34.1; 189.00 ng/mL for THS 2.2 Menthol arm and 231.72 ng/mL for the mCC arm) lower, respectively, for the THS 2.2 Menthol arm compared to the mCC arm. The median  $t_{peak}$  on Day 5 was similar for the THS 2.2 Menthol and mCC arms for both nicotine (14.97 versus 13.03 hours, respectively) and cotinine (16 hours for both arms).

#### Cytochrome P450 1A2 Activity

On Day 5, CYP1A2 activity had decreased from baseline by approximately 33% and 35% in the THS 2.2 Menthol and SA arms, respectively; while in the mCC arm, CYP1A2 activity had increased from baseline by approximately 4%. During the Ambulatory Period, CYP1A2 activity remained decreased with a 32% and 35% change from baseline in the THS 2.2 Menthol and SA arms, respectively, and a decrease from baseline in the mCC arm of 17% on Day 90.

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 36% (95% CI: 30.8, 41.7) lower than subjects who continued to smoke mCC on Day 5 and 21% lower (95% CI: 7.0, 33.6) 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: 92.1, 111.9 on Day 5; 105%; 95% CI: 80.5, 137.9 on Day 90).





### Extent of Exposure – Product Use Consumption

During the Confinement Period, for the PP Sets, at baseline (Day 0) the mean number of mCC consumed daily in the THS 2.2 Menthol and mCC arms (Period 1) was 12.2 (95% CI: 11.3, 13.1) and 12.2 (95% CI: 11.1, 13.3) cigarettes/day, respectively. During the Confinement Period, the number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm increased from a mean of 12.5 (95% CI: 11.4, 13.6) sticks/day on Day 1 to 16.5 (95% CI: 15.1, 17.9) sticks/day on Day 5. The mean number of mCC consumed daily was stable throughout the Confinement Period at 11.3 (95% CI: 10.1, 12.5) to 13.7 (95% CI: 12.2, 15.1) sticks/day on Day 1 and Day 5, respectively.

During the Ambulatory Period, for the PP Sets, the mean number of THS Menthol Tobacco Sticks consumed daily in the THS 2.2 Menthol arm was lower than Day 5 but higher than the number of mCC consumed at baseline, with a mean 14.7 (95% CI: 12.8, 16.7), 15.2 (95% CI: 12.9, 17.4), and 14.2 (95% CI: 12.1, 16.3) sticks/day reported during Periods 2, 3, and 4, respectively. In the mCC arm, the mean number of mCC/CC consumed daily during the Ambulatory Period remained higher than consumed at baseline, with a mean 15.5 mCC/day (95% CI: 13.4, 17.7) reported during Period 4. For each product use period in the Ambulatory Period, the mean reported daily number of THS Menthol Tobacco Sticks was slightly lower than the daily product use in the mCC arm.

For both the Safety Population and the PP Sets, during the Ambulatory Period the number of THS Menthol Tobacco Sticks used in the THS 2.2 Menthol arm and number of mCC/CC used in the mCC arm was relatively stable. The average reported daily number of THS Menthol Tobacco Sticks used in the THS 2.2 Menthol arm was higher in the PP Set across the Ambulatory Visits (14.2 to 15.2 sticks/day) compared to the Safety Population (11.7 to 12.9 sticks/day), and was comparable to the average daily number of mCC/CC used in the Safety Population (15.0 to 15.8 sticks/day) and PP Set (14.9 to 15.5 sticks/day) for the mCC arm.

### Compliance to Investigational Product and Product Use

Compliance to arm allocation was calculated for the PP Sets. During Confinement, full compliance was examined for the THS 2.2 Menthol and mCC arms based on the product distribution log. Five subjects in the THS 2.2 Menthol arm and 6 subjects in the mCC arm were excluded from the PP Set Population during the Confinement due to major deviations including misrandomization. Out of the 75 subjects in the THS 2.2 Menthol arm and 35 subjects in the mCC arm in the PP Set Population, all were exclusively using their allocated product during Confinement. For subjects in the SA arm, the abstinence during Confinement was verified daily using an exhaled CO breath test: Of 39 subjects in the SA arm, 6 subjects had CO breath test above 10 ppm, the cut-off point used to assess SA; all but 1 value above 10 ppm occurred on Day 6 and were excluded from the PP Set



Population; 24 subjects had no CO breath test value above 10 ppm after Day 1 during Confinement.

During the Ambulatory Period, full compliance was examined for THS 2.2 Menthol and mCC arms based on product consumption as recorded in their electronic diary. Thirty-two, 36, and 41 subjects in Periods 2, 3, and 4, respectively, for THS 2.2 Menthol arm were exclusively using THS 2.2 Menthol. One subject in the mCC arm was using another product in addition to mCC/CC during Periods 3 and 4. All other subjects were exclusively using mCC/CC during the Ambulatory Period. For subjects in the SA arm, the abstinence during the Ambulatory Period was verified daily based on product consumption as recorded in their electronic diary and verified chemically using an exhaled CO breath test on Day 30, Day 60, and Day 90 Visits. The cut-off point for the CO breath test value for abstinence was 10 ppm. Eight, 7, and 7 subjects in Periods 2, 3 and 4 were categorized as fully abstinent.

*Risk Markers (Clinical Risk Markers; CREs)*

***Risk Marker of Oxidative Stress: 8-epi-PGF<sub>2α</sub> (Concentration Adjusted for Creatinine) (Day 90)***

The levels of 8-epi-PGF<sub>2α</sub> in subjects who switched to THS 2.2 Menthol were 14% (95% CI: 2.0, 23.6) 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 (geometric mean ratio: 95%; 95% CI: 77.7, 115.1).

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

There were no notable differences in levels of 11-DTX-B2 between subjects who switched to THS 2.2 Menthol and those who continued to smoke mCC (96% ratio; 95% CI: 75.4, 123.3) and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking (geometric mean ratio: 104%; 95% CI: 70.4, 153.2).

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

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol were 11% (95% CI: 4.0, 16.7) lower than those 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 (geometric mean ratio: 99%; 95% CI: 88.7, 111.1).



***Risk Markers of Lipid Metabolism: HDL Cholesterol, LDL Cholesterol, Triglycerides, Total Cholesterol, and Apolipoprotein A1 and B (Day 90 or Day 91/Discharge from the Ambulatory Period)***

There were no notable differences observed in the levels of HDL-C (1.37 difference; 95% CI: -2.26, 5.00), LDL-C (-3.31 difference; 95% CI: -11.96, 5.34), TC (-4.05 difference; 95% CI: -13.29, 5.19), Apo A1 (3.05 difference; 95% CI: -4.57, 10.67), and Apo B (-1.60 difference; 95% CI: -7.24, 4.03) as well as TG (0.89 difference; 95% CI: -12.72, 14.51) between subjects who switched to THS 2.2 Menthol use, subjects who continued to smoke mCC, and to subjects who abstained from smoking.

***Risk Markers of Inflammation: Platelets and White Blood Cell Differential Counts (Day 91/Day of Discharge from the Ambulatory Period)***

The ratios of platelet counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (geometric mean ratio: 103%; 95% CI 96.3, 111.2) and as well as subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking (geometric mean ratio: 102%; 95% CI: 91.1, 114.5) remained comparable over the study period.

There were no notable differences observed in the total WBC (leukocytes) counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (0.2 GI/L difference; 95% CI: -0.5, 0.8). Total WBC (leukocytes) count was higher by 1.1 GI/L for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.1, 2.2).

Similarly, no notable differences were observed in neutrophil levels between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (0.0 GI/L difference; 95% CI: -0.5, 0.6). Neutrophil levels were higher by 1.0 GI/L for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.2, 1.9).

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, hs-CRP and fibrinogen, the levels observed between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and subjects who abstained from smoking remained similar.



***Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure (Day 91/Day of Discharge from the 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, Hemoglobin A1c, Body Weight, and Waist Circumference (Day 90 or Day 91/Day of Discharge from the Ambulatory Period)***

For subjects who switched to THS 2.2 Menthol and subjects who continued smoking mCC as well as between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking, levels observed remained similar.

***Risk Markers for Respiratory Diseases: Lung Function***

In the PP Set (Period 4), there were no notable differences on Day 91/Discharge Ambulatory in gas transfer parameters (DLCO and KCO), lung volume parameters (FRV, TLC, and IC), or spirometry parameters (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and MEF 25-75) between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. On Day 91/Discharge Ambulatory, VC was 0.1 L higher in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC (95% CI: 0.0, 0.2).

Based on 7 to 9 subjects available for analyses in the SA arm, there were no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at both Day 6/Discharge Confinement and Day 91/Discharge Ambulatory in all lung function parameters, except for FRV and IC which were 0.5 L (95% CI: 0.1, 0.8) lower and 0.9 L (95% CI: 0.4, 1.3) higher on Day 91/Discharge/Ambulatory in subjects who switched to THS 2.2 Menthol compared to subjects who abstained from smoking.

**Exploratory Endpoints****Ames Mutagenicity Test**

At baseline, mean Ames mutagenicity test values were comparable between the THS 2.2 Menthol and SA arms (30251.24 and 28259.41 REV/24h, respectively) and lower in the mCC arm (14508.13 REV/24h). On Day 5, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values had decreased by approximately 72% and 62%, respectively. In the mCC arm, Ames mutagenicity test values (REV/24h) showed a mean increase from baseline of approximately 47%. Consistent results were also observed in



median values, with Day 5 values of 70% and 85% lower than baseline in the THS 2.2 Menthol and SA arms, respectively, and 76% higher than baseline in the mCC arm.

#### Cytochrome P450 2A6 Activity

At baseline, CYP2A6 activity was comparable between study arms (range of 28% to 30%). There was no notable difference in CYP2A6 activity on Day 6/Discharge Confinement between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (95% CI: 95.2, 117.3). On Day 6/Discharge Confinement, the CYP2A6 activity was approximately 57% lower (95% CI: 52.1, 62.3) in subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking.

There was no notable difference in CYP2A6 activity on Day 90 between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (95% CI: 81.4, 106.6). On Day 90, the LS mean of CYP2A6 activity following THS 2.2 Menthol use was 37% lower than the activity observed in subjects who abstained from smoking (95% CI: 22.4, 49.3).

#### Fagerström Test for Nicotine Dependence on Day 90

On Day 90, a decrease in FTND severity was observed for a number of subjects in both the THS 2.2 Menthol and mCC arms, with 9 subjects (19%) in the THS 2.2 Menthol arm and 4 subjects (13%) in the mCC arm shifting from moderate to mild dependency, and 11 subjects (23%) in the THS 2.2 Menthol arm and 6 subjects (19%) in the mCC arm shifting from severe to moderate dependency. Four subjects in each of the THS 2.2 Menthol and mCC arms reported a worsening of nicotine dependence on Day 90, with 2 subjects (4%) in the THS 2.2 Menthol arm and 2 subjects (6%) in the mCC arm shifting from mild to moderate, and 2 subjects in the THS 2.2 Menthol arm and 2 subjects in the mCC arm shifting from moderate to severe. There were only 4 subjects in the SA arm for the PP Set on Day 90, with all subjects categorized as mild.

#### Urge-to-smoke Symptoms (QSU-brief)

The average urge-to-smoke total scores were comparable between study arms at baseline. During the Confinement Period, the average urge-to-smoke total scores remained stable for the THS 2.2 Menthol and mCC arms (3.78 to 3.93 for the THS 2.2 Menthol arm and 3.86 to 4.13 for the mCC arm; ranges of individual scores were 1.0 to 7.0 for both arms). 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 the 95% CI for all parameters spanning 0. There were no notable differences between the QSU-brief urge-to-smoke total score, Factor 1 score, or Factor 2 score on Day 5 for the subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking, with 95% CIs for all parameters spanning 0.





During the Ambulatory Period, the average urge-to-smoke total scores were stable for the THS 2.2 Menthol and mCC arms. 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 the 95% CI for all parameters spanning 0 during the Ambulatory Period. The urge-to-smoke overall and factor scores of subjects who switched to THS 2.2 Menthol use were higher than those subjects who abstained from smoking, with differences of 1.3 points (95% CI: 0.5, 2.2), 1.7 points (95% CI: 0.7, 2.8), and 0.9 points (95% CI: 0.0, 1.7) 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 -0.15 on Day 6/Discharge Confinement (95% CI: -0.4, 0.1). For the comparison of THS 2.2 Menthol against SA the urge to smoke was higher in the SA arm and steadily decreased, with differences of -0.57 (95% CI: -0.8, -0.3), -0.45 (95% CI: -0.7, -0.2), -0.36 (95% CI: -0.6, -0.1), and -0.19 (95% CI: -0.5, 0.1) reported on Days 2, 3, 4, and 5, respectively. By Day 6/Discharge Confinement the difference was similar to that observed for the comparison of THS 2.2 Menthol and mCC, with a difference of -0.12 (95% CI: -0.4, 0.1).

During the Ambulatory Period, the differences of THS 2.2 Menthol – mCC for MNWS-R total scores remained stable, with a difference of -0.08 on Day 90 (95% CI: -0.3, 0.2). The differences of THS 2.2 Menthol – SA for MNWS-R total scores also remained stable, with a difference of 0.17 on Day 90 (95% CI: -0.2, 0.5).

#### Product Evaluation Questionnaire (MCEO)

Craving reduction (THS m2.2 – mCC difference: -1.1; 95% CI: -1.8, -0.4), enjoyment of respiratory tract sensation (difference: -0.6; 95% CI: -1.3, 0.1), and smoking satisfaction (difference: -1.0; 95% CI: -1.5, -0.4) were all lower for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC.

Difference Between THS 2.2 Menthol and mCC Scores for MCEQ Subscales – PP Set		
MCEQ Subscale/Time point	Difference THS 2.2 Menthol - mCC	
	Difference	95% CI
Aversion		
Day 1	-0.10	-0.47, 0.28
Day 5	0.15	-0.20, 0.49
Day 90	0.08	-0.18, 0.34
Craving reduction		



Day 1	-1.6	-2.3, -0.9
Day 5	-1.1	-1.8, -0.4
Day 90	-0.7	-1.4, 0.0
Enjoyment of respiratory tract sensation		
Day 1	-1.1	-1.7, -0.4
Day 5	-0.6	-1.3, 0.1
Day 90	-0.2	-0.8, 0.5
Psychological reward		
Day 1	-0.91	-1.38, -0.45
Day 5	-0.40	-0.86, 0.06
Day 90	-0.30	-0.78, 0.17
Smoking satisfaction		
Day 1	-1.46	-2.03, -0.89
Day 5	-0.96	-1.50, -0.42
Day 90	-0.37	-0.88, 0.13
Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol.		

Over the course of the study, these differences between the THS 2.2 Menthol and mCC arms for the craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction subscales reduced so that there were no notable differences observed for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (difference of 0.1 [95% CI: -0.2, 0.3] for aversion; difference of -0.2 [95% CI: -0.8, 0.5] for enjoyment of respiratory tract sensation; and difference of -0.4 [95% CI: -0.9, 0.1] for smoking satisfaction MCEQ subscales). Craving reduction was still notably lower on Day 90 but less of a difference than on Day 5 (THS m2.2 – mCC difference: -0.7; 95% CI: -1.4, 0.0).

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 the aversion and psychological reward subscales.

#### Oxysterol Assessments

For all 5 $\alpha$ ,6 $\alpha$ -epoxycholestanol, 7-ketocholesterol, 7 $\beta$ -hydroxycholesterol, 5 $\beta$ ,6 $\beta$ -epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 22(R)-hydroxycholesterol, 4 $\beta$ -hydroxycholesterol, 27-hydroxycholesterol, and cholesterol, the mean values were comparable to baseline on Days 6 and 90 for all study arms.



### Human Smoking Topography

Total puff volume for the THS 2.2 Menthol arm increased from baseline to Day 1 and reached its maximum on Day 4, in contrast to what was observed for mCC. This was mainly driven by an increase of average puff volume and the total number of puffs. The THS 2.2 Menthol versus mCC total puff volume exhibited a difference of approximately 187 mL at Day 4. The total puff volume subsequently decreased during the Ambulatory Period in the THS 2.2 Menthol arm. However a similar decrease was observed in the mCC arm eventually resulting in a THS 2.2 Menthol and mCC volume of 792.98 mL and 623.15 mL, respectively, in subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (169.84 mL difference; 95% CI: -69.94, 409.61).

Average puff volume and average puff duration was comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with a 0.12 mL (95% CI: -11.29, 11.05) and 0.32 mL (95% CI: -0.08, 0.71) difference, respectively. In contrast, average flow was 7.41 mL/s lower in subjects who continued to smoke mCC (95% CI: 1.65, 13.18).

The THS 2.2 Menthol users increased the total number of puffs compared to subjects in the mCC arm (3.34 puffs difference; 95% CI: 0.13, 6.81). The total smoking duration was approximately 1.5 minutes lower for subjects who switched to smoking THS 2.2 Menthol compared to subjects who continued to smoke mCC (-88.62 s difference; 95% CI: -146.88, -30.36) while an increase in puff frequency of 2.22 puffs/min (95% CI: 0.55, 3.90) was observed in subjects using THS 2.2 Menthol in comparison with subjects who continued to smoke mCC. These changes were the result of a process of adaptation following the switch to THS 2.2 Menthol.

### Prochaska 'Stage of Change' Questionnaire Results

At baseline in the FAS, all subjects were current smokers and only 1 smoker in the mCC arm was thinking of quitting in the next 30 days. The majority of subjects in the THS 2.2 Menthol, mCC, and SA arms had never tried to quit smoking (81%, 83%, and 67% of subjects, respectively).

On Day 90, all subjects in the THS 2.2 Menthol and mCC arms for the FAS classed themselves as a current smoker (67 and 29 subjects, respectively), while 6 subjects in the SA arm (21%) reported they had quit smoking in the last 6 months, and 23 subjects (79%) classed themselves as current smokers. The majority of subjects in the THS 2.2 Menthol, mCC, and SA arms were not thinking of quitting on Day 90 (78%, 83%, and 64% of subjects, respectively) while 10%, 14%, and 28% of subjects, respectively, were thinking of quitting in the next 30 days, and 12%, 3%, and 8%, respectively, were thinking of quitting in the next 6 months.





### Visual Inspection of the THS Tobacco Plugs and Filter Analysis

On all study days, the majority of THS Tobacco Plugs ( $\geq 98.7\%$  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 0.2% to 1.2%). There were only 2 occurrences among greater than 5600 THS Tobacco Plugs analyzed reported as showing ashes inside the tobacco plug and burnt paper (grade 2) following visual inspection.

Visual inspection of THS Menthol Tobacco Plugs was possible for the majority of plugs on Days 30, 60, and 90 ( $>99\%$  each day; approximately 789 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 0.1% to 0.9%). There were no occurrences of a grade 2.

### Biomarkers of Exposure in 4-hour Urine Fractions

The scatter plots showed good correlation between BoExp concentrations adjusted for creatinine from 24-hour urine collection and the 4-hour urine fractions at baseline and Day 90 and the Bland-Altman plots also showed good concordance between the results of the 24-hour collections and the 4-hour fractions, with geometric mean 24-hour: 4-hour ratios varying between 85% and 138%.

### **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 51% to 96% lower) and Day 90 (full range was 34% to 86% lower). The magnitude of reduction observed was similar to that observed in the SA arm for these BoExp, except for 3-HPMA, Total NNN, o-toluidine, and B[a]P. 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-C: lipid pathway; 8-epi-PGF<sub>2α</sub>: oxidative stress; 11-DTX-B2: platelet activation; sICAM-1: endothelial dysfunction; WBC (leukocytes) count: inflammation; VC: lung function parameter). 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 compared to continuing smoking mCC 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. 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, with no notable difference observed on Day 6/Discharge Confinement. For the MCEQ subscales, 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 SA arms reducing over time during the study for subscales such as craving reduction and smoking satisfaction.





## 12 SAFETY EVALUATIONS

The safety endpoints were analyzed using the Safety Population. The overall Safety Population contained 165 subjects: 160 randomized subjects and 5 subjects who were exposed to THS 2.2 Menthol at the product test but were not randomized; these data are included on the pre-randomization tables. The post-randomization Safety Population consisted of 160 randomized subjects (80 subjects in the THS 2.2 Menthol arm, 41 subjects in the mCC arm, and 39 subjects in the SA arm).

### 12.1 Adverse Events

#### 12.1.1 Brief Summary of Adverse Events

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](#). A summary of AEs during the pre-randomization period are presented in [Table 129](#). A summary of AEs reported post-randomization (Confinement and Ambulatory Periods) by study arm are also presented in [Table 130](#). 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](#) and are also presented in [Table 131](#).

**Table 129 Summary of Adverse Events (Safety Population) – Pre-Randomization**

	Study Arm			Product Test only (N=5)	Overall Safety (N=165)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)		
Number of:					
AEs	38	16	18	12	84
SAEs	0	0	0	2	2
Severe AEs	0	0	0	3	3
AEs leading to discontinuation	0	0	0	2	2
AEs related to IP	1	0	0	0	1
AEs related to study procedures	8	4	3	5	20
Number (%) of subjects with:					
AEs	33 (41.3%)	11 (26.8%)	14 (35.9%)	4 (80.0%)	62 (37.6%)
AEs related to IP	1 (1.3%)	0	0	0	1 (0.6%)
AEs related to study procedures	5 (6.3%)	3 (7.3%)	3 (7.7%)	2 (40.0%)	13 (7.9%)

Abbreviations: AE = adverse event; mCC = Menthol conventional cigarette; IP = investigational product; 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 in the column headers.

Data Source: [Appendix 15, Table 15.2.6.1](#) and [15.2.6.7](#).

**Table 130 Summary of Adverse Events (Safety Population) – Post-Randomization**

	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	
Number of:				
AEs	114	32	49	195
SAEs	0	0	0	0
Severe AEs	8	2	2	12
AEs leading to discontinuation	0	0	0	0
AEs related to IP	7	1	0	8
AEs related to study procedures	3	2	2	7
Number (%) of subjects with:				
AEs	52 (65.0%)	20 (48.8%)	23 (59.0%)	95 (59.4%)
AEs related to IP	7 (8.8%)	1 (2.4%)	0	8 (5.0%)
AEs related to study procedures	3 (3.8%)	2 (4.9%)	2 (5.1%)	7 (4.4%)

Abbreviations: AE = adverse event; mCC = Menthol conventional cigarette; IP = investigational product; 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 in the column headers.

Data Source: [Appendix 15, Table 15.2.6.1](#).

**Table 131 Summary of Adverse Events (Safety Population) by Product Use Category – Ambulatory Period**

	Within THS m2.2 (N=80)			Within mCC (N=41)		Within SA (N=39)	
	THS m2.2 (N=67)	Dual (N=10)	CC (N=3)	CC (N=40)	Abstinent (N=6)	Predominantly abstinent (N=4)	Not abstinent (N=24)
Number of:							
AEs	60	8	6	18	2	4	16
SAEs	0	0	0	0	0	0	0
Severe AEs	8	0	0	2	1	0	1
AEs leading to discontinuation	0	0	0	0	0	0	0
AEs related to IP	2	0	0	0	0	0	0
AEs related to study procedures	0	1	0	0	0	0	0
Number (%) of subjects with:							
AEs	32 (47.8%)	6 (60.0%)	3 (100%)	14 (35.0%)	1 (16.7%)	2 (50.0%)	11 (45.8%)
AEs related to IP	2 (3.0%)	0	0	0	0	0	0
AEs related to study procedures	0	1 (10.0%)	0	0	0	0	0

Abbreviations: AE = adverse event; mCC = Menthol conventional cigarette; IP = investigational product; 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 in the column headers.

Data Source: [Appendix 15, Table 15.2.6.2.](#)



Two SAEs were reported by 1 subject who was enrolled but not randomized. There were no SAEs reported in the post-randomization period. 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 129](#)). The 2 subjects experienced AEs of procedural complication and syncope ([Appendix 15, Table 15.2.6.7](#)). Three severe AEs were reported in the pre-randomization period by 2 subjects who were enrolled but not randomized. Twelve severe AEs were reported in the post-randomization period, all of which were reported in the Ambulatory Period. Details of the SAEs are presented in [Section 12.2](#) and details of severe AEs are presented in [Section 12.1.3.1](#).

Prior to randomization there were 84 AEs reported in 62 of 165 subjects (37.6%) with the majority of AEs classed as mild. Post-randomization, 195 AEs were reported by 95 of the 160 subjects (59.4%) in the Safety Population.

The incidence of post-randomization AEs ([Table 130](#)) was comparable in the THS 2.2 Menthol arm (52 of 80 subjects [65.0%]) and the SA arm (23 of 39 subjects [59.0%]), and slightly lower in the mCC arm (20 of 41 subjects [48.8%]). Similarly, the frequency of AEs was comparable in the THS 2.2 Menthol arm (114 AEs from 80 subjects) and the SA arm (49 AEs from 39 subjects), and slightly lower in the mCC arm (32 AEs from 41 subjects).

The majority of subjects in the THS 2.2 arm were classed as predominantly users of THS 2.2 Menthol (67 of 80 subjects) and so the majority of AEs were reported by these subjects (60 of 74 AEs) ([Table 131](#)). The incidence of AEs was higher in subjects who were dual users (60.0%) and CC users (100%) than primarily THS 2.2 Menthol users (47.8%), though there were a small number of subjects in the dual users (N=10) and CC users (N=3) product use categories.

During the study, only 8 AEs reported by 8 subjects (5.0%) were considered related to the IP; 7 AEs reported by 7 subjects (8.8%) in the THS 2.2 Menthol arm and 1 AE reported by 1 subject (2.4%) in the mCC arm. The 7 related AEs reported in the THS 2.2 Menthol arm were not expected while the related AE in the mCC arm was expected.

### 12.1.2 Display of Adverse Events

Adverse events are summarized by study arm for the Safety Population by SOC and PT in [Appendix 15, Table 15.2.6.3](#). A summary of AEs by SOC and PT are also provided in [Table 132](#) for the post-randomization period. 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](#).



**Table 132 Summary of Adverse Events by System Organ Class and Preferred Term For PT reported by  $\geq 2$  subjects (Safety Population) – Post-randomization**

System Organ Class Preferred Term	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	
Number (%) of subjects with any AEs	52 (65.0%)	20 (48.8%)	23 (59.0%)	95 (59.4%)
Gastrointestinal disorders	15 (18.8%)	2 (4.9%)	3 (7.7%)	20 (12.5%)
Abdominal pain	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Constipation	3 (3.8%)	0	0	3 (1.9%)
Dry mouth	2 (2.5%)	0	1 (2.6%)	3 (1.9%)
Lip dry	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Nausea	3 (3.8%)	0	1 (2.6%)	4 (2.5%)
Toothache	2 (2.5%)	0	1 (2.6%)	3 (1.9%)
Infections and infestations	5 (6.3%)	5 (12.2%)	1 (2.6%)	11 (6.9%)
Upper respiratory tract infection	3 (3.8%)	4 (9.8%)	1 (2.6%)	8 (5.0%)
Injury, poisoning, and procedural complications	5 (6.3%)	4 (9.8%)	3 (7.7%)	12 (7.5%)
Administration related reaction	0	2 (4.9%)	0	2 (1.3%)
Ligament sprain	3 (3.8%)	0	0	3 (1.9%)
Muscle strain	0	0	2 (5.1%)	2 (1.3%)
Investigations	27 (33.8%)	11 (26.8%)	12 (30.8%)	50 (31.3%)
Aspartate aminotransferase increased	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Blood bilirubin increased	1 (1.3%)	0	1 (2.6%)	2 (1.3%)
Blood potassium increased	2 (2.5%)	1 (2.4%)	0	3 (1.9%)
Blood triglycerides increased	2 (2.5%)	2 (4.9%)	2 (5.1%)	6 (3.8%)
Forced expiratory volume decreased	2 (2.5%)	0	0	2 (1.3%)
Haemoglobin decreased	11 (13.8%)	4 (9.8%)	6 (15.4%)	21 (13.1%)
Lymphocyte count increased	6 (7.5%)	2 (4.9%)	1 (2.6%)	9 (5.6%)
Neutrophil count decreased	4 (5.0%)	0	0	4 (2.5%)
Vital capacity decreased	2 (2.5%)	0	0	2 (1.3%)
Carbon monoxide diffusing capacity decreased	1 (1.3%)	1 (2.4%)	1 (2.6%)	3 (1.9%)
Metabolism and nutrition disorders	2 (2.5%)	0	2 (5.1%)	4 (2.5%)
Hypertriglyceridaemia	2 (2.5%)	0	0	2 (1.3%)
Musculoskeletal and connective tissue disorders	2 (2.5%)	0	1 (2.6%)	3 (1.9%)
Back pain	1 (1.3%)	0	1 (2.6%)	2 (1.3%)
Nervous system disorders	7 (8.8%)	1 (2.4%)	4 (10.3%)	12 (7.5%)
Dizziness	1 (1.3%)	0	2 (5.1%)	3 (1.9%)
Headache	4 (5.0%)	1 (2.4%)	3 (7.7%)	8 (5.0%)
Renal and urinary disorders	1 (1.3%)	0	3 (7.7%)	4 (2.5%)
Glycosuria	1 (1.3%)	0	1 (2.6%)	2 (1.3%)
Respiratory, thoracic, and mediastinal disorders	9 (11.3%)	4 (9.8%)	3 (7.7%)	16 (10.0%)
Cough	3 (3.8%)	1 (2.4%)	0	4 (2.5%)
Nasal congestion	3 (3.8%)	2 (4.9%)	0	5 (3.1%)
Oropharyngeal pain	2 (2.5%)	0	1 (2.6%)	3 (1.9%)
Sinus congestion	1 (1.3%)	0	1 (2.6%)	2 (1.3%)

**Table 132 Summary of Adverse Events by System Organ Class and Preferred Term For PT reported by  $\geq 2$  subjects (Safety Population) – Post-randomization (continued)**

System Organ Class Preferred Term	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	
Skin and subcutaneous tissue disorders	3 (3.8%)	1 (2.4%)	2 (5.1%)	6 (3.8%)
Acne	2 (2.5%)	0	0	2 (1.3%)
Pruritus	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Rash	2 (2.5%)	1 (2.4%)	0	3 (1.9%)

Abbreviations: AE = adverse event; mCC = Menthol conventional cigarette; N = number of subjects; PT = preferred term; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol. Terms coded using MedDRA<sup>®</sup> version 16.0.

Percentages were calculated using the N in the column headers.

Data Source: [Appendix 15, Table 15.2.6.3](#).

Overall, the most common AEs by SOC were Investigations (reported by 27 of 80 subjects [33.8%] in the THS 2.2 Menthol arm, 11 of 41 subjects [26.8%] in the mCC arm, and 12 of 39 subjects [30.8%] in the SA arm); Gastrointestinal Disorders (reported by 15 of 80 subjects [18.8%] in the THS 2.2 Menthol arm, 2 of 41 subjects [4.9%] in the mCC arm, and 3 of 39 subjects [7.7%] in the SA arm); and Respiratory, Thoracic, and Mediastinal Disorders (reported by 9 of 80 subjects [11.3%] in the THS 2.2 Menthol arm, 4 of 41 subjects [9.8%] in the mCC arm, and 3 of 39 subjects [7.7%] in the SA arm). All other AEs by SOC were reported in <10% subjects overall.

The most common AEs by PT were hemoglobin decreased (reported by 11 of 80 subjects [13.8%] in the THS 2.2 Menthol arm, 4 of 41 subjects in the mCC arm [9.8%], and 6 of 39 subjects [15.4%] in the SA arm); lymphocyte count increased (reported by 6 of 80 subjects [7.5%] in the THS 2.2 Menthol arm, 2 of 41 subjects in the mCC arm [4.9%], and 1 of 39 subjects [2.6%] in the SA arm); upper respiratory tract infection (reported by 3 of 80 subjects [3.8%] in the THS 2.2 Menthol arm, 4 of 41 subjects in the mCC arm [9.8%], and 1 of 39 subjects [2.6%] in the SA arm); and headache (reported by 4 of 80 subjects [5.0%] in the THS 2.2 Menthol arm, 1 of 41 subjects in the mCC arm [2.4%], and 3 of 39 subjects [7.7%] in the SA arm). All other AEs by were reported in <5% of subjects overall.

### 12.1.3 Analysis of Adverse Events

#### 12.1.3.1 Analysis of Adverse Events by Severity

Adverse events are summarized by severity (mild, moderate, or severe), SOC, and PT for the Safety Population by study arm in [Appendix 15, Table 15.2.6.10](#), and by severity, product use category, SOC, and PT for the Safety Population by study arm in [Appendix 15, Table 15.2.6.11](#).



The majority of AEs reported during the study were mild in severity. In the pre-randomization period, 66 of the 84 reported AEs were mild in severity, 15 were moderate and 3 were classed as severe. The 3 severe AEs were reported by 2 subjects who were enrolled but not randomized into the study. Subject 1119 reported severe AEs of diabetic ketoacidosis and sinusitis which were also considered serious. Further details are presented in [Section 12.2.2](#). Subject 1233 reported a severe AE of syncope which was related to study procedures.

An overview of AE severity for the post-randomization period is shown in [Table 133](#).

**Table 133 Overview of Adverse Event Severity (Safety Population)**

System Organ Class Preferred Term	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	
Number (%) subjects with any AEs	52 (65.0%)	20 (48.8%)	23 (59.0%)	95 (59.4%)
Mild	33 (41.3%)	16 (39.0%)	16 (41.0%)	65 (40.6%)
Moderate	23 (28.8%)	8 (19.5%)	10 (25.6%)	41 (25.6%)
Severe	8 (10.0%)	2 (4.9%)	2 (5.1%)	12 (7.5%)

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

Percentages were calculated using the N in the column headers.

Data Source: [Appendix 15, Table 15.2.6.1](#).

There were no severe AEs during the Confinement Period. In the Ambulatory Period, 12 severe AEs were reported by 12 subjects; 8 in the THS 2.2 Menthol arm, 2 in the mCC arm, and 2 in the SA arm. All severe AEs were due to findings in clinical laboratory evaluations. Of the 12 severe AEs, 9 were due to decreased hemoglobin (5 in the THS 2.2 Menthol arm and 2 in both the mCC and SA arms). Severe AEs of increased GGT, hypertriglyceridemia, and glucosuria were also reported in the THS 2.2 Menthol arm. Further details of the severe AEs in the Ambulatory Period are presented in [Section 12.3](#).

### 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](#), and by product use category, SOC, and PT in [Appendix 15, Table 15.2.6.6](#).

In the pre-randomization period, only 1 of the 84 reported AEs was assessed as related to IP use; an AE of dizziness reported by Subject 1125 (THS 2.2 Menthol arm).





Adverse events related to IP use during the Confinement and Ambulatory Periods are summarized by PT in [Table 134](#).

**Table 134 Summary of Adverse Events Related to Investigational Product by Preferred Term (Safety Population)**

Preferred Term	Study Arm			Overall Safety (N=160)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	
Number (%) subjects with any AEs related to IP	7 (8.8%)	1 (2.4%)	0	8 (5.0%)
Dry mouth	1 (1.3%)	0	0	1 (0.6%)
Salivary hypersecretion	1 (1.3%)	0	0	1 (0.6%)
Carbon monoxide diffusing capacity decreased	1 (1.3%)	1 (2.4%)	0	2 (1.3%)
Sneezing	1 (1.3%)	0	0	1 (0.6%)
Upper airway cough syndrome	1 (1.3%)	0	0	1 (0.6%)
Non-cardiac chest pain	1 (1.3%)	0	0	1 (0.6%)
Cough	1 (1.3%)	0	0	1 (0.6%)

Abbreviations: AE = adverse event; IP = investigational product; mCC = conventional cigarette; N = number of subjects; 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 in the column headers.

Data Source: [Appendix 15, Table 15.2.6.5](#).

Eight AEs assessed as related to IP use were reported by 8 of the 160 subjects; 7 in the THS 2.2 Menthol arm and 1 subject in the mCC arm. All related AEs were mild in severity. Carbon monoxide diffusing capacity decreased was the only AE observed in more than 1 subject. All 7 AEs in the THS 2.2 arm were assessed as not expected, while the AE in the mCC arm was assessed as expected.

#### 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](#). Adverse events related to study procedures for the pre-randomization period are summarized in [Table 135](#).

**Table 135 Summary of Adverse Events Related to Study Procedures by Preferred Term - Pre-randomization Period (Safety Population)**

System Organ Class Preferred Term	Study Arm				Overall Safety (N=165)
	THS m2.2 (N=80)	mCC (N=41)	SA (N=39)	Product Test (N=5)	
Number (%) subjects with any AEs related to study procedures	5 (6.3%)	3 (7.3%)	3 (7.7%)	2 (40.0%)	13 (7.9%)
Gastrointestinal disorders	1 (1.3%)	1 (2.4%)	1 (2.6%)	0	3 (1.8%)
Abdominal pain	0	1 (2.4%)	0	0	1 (0.6%)
Dyspepsia	1 (1.3%)	0	0	0	1 (0.6%)
Flatulence	0	0	1 (2.6%)	0	1 (0.6%)
Nausea	0	1 (2.4%)	0	0	1 (0.6%)
General disorders and administration site conditions	1 (1.3%)	1 (2.4%)	0	0	2 (1.2%)
Induration	1 (1.3%)	0	0	0	1 (0.6%)
Vessel puncture site bruise	1 (1.3%)	0	0	0	1 (0.6%)
Vessel puncture site haemorrhage	0	1 (2.4%)	0	0	1 (0.6%)
Injury, poisoning, and procedural complications	0	1 (2.4%)	1 (2.6%)	1 (20.0%)	3 (1.8%)
Administration related reaction	0	1 (2.4%)	0	0	1 (0.6%)
Excoriation	0	0	0	1 (20.0%)	1 (0.6%)
Procedural complication	0	0	0	1 (20.0%)	1 (0.6%)
Procedural hypotension	0	0	1 (2.6%)	0	1 (0.6%)
Musculoskeletal and connective tissue disorder	1 (1.3%)	0	0	0	1 (0.6%)
Pain in extremity	1 (1.3%)	0	0	0	1 (0.6%)
Nervous system disorders	4 (5.0%)	0	1 (2.6%)	1 (20.0%)	6 (3.6%)
Presyncope	1 (1.3%)	0	1 (2.6%)	0	2 (1.2%)
Syncope	3 (3.8%)	0	0	1 (20.0%)	4 (2.4%)
Respiratory, thoracic, and mediastinal disorders	0	0	0	1 (20.0%)	1 (0.6%)
Epistaxis	0	0	0	1 (20.0%)	1 (0.6%)

Abbreviations: AE = adverse event; mCC = Menthol conventional cigarette; N = number of subjects;

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 in the column headers.

Data Source: [Appendix 15, Table 15.2.6.9](#).

Twenty AEs related to study procedures were reported by 13 subjects in the pre-randomization period. Presyncope and syncope were the most common study procedure related AEs, reported by 2 and 4 subjects, respectively. All other study procedure related AEs were only reported by 1 subject in the pre-randomization period.





Six AEs related to study procedures were reported by 6 subjects in the Confinement Period. Two subjects in the mCC arm reported AEs of administration related reaction and 1 subject in each of the THS 2.2 Menthol and SA arms reported an AE of dizziness. All other study procedure related AEs were only reported by 1 subject in the Confinement Period.

Only one study procedure related AE was reported in the Ambulatory Period, an AE of nausea in the THS 2.2 Menthol arm.

#### 12.1.4 Listing of Adverse Events by Subject

Adverse events are listed by subject in [Appendix 15, Listing 15.3.6.1](#).

#### 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 15.3.6.5](#). Device events and malfunctions are summarized by study arm for the Safety Population in [Appendix 15, Table 15.2.6.15](#).

One major device event was reported in the pre-randomization period, an event of “device inoperable” which was not related to an AE.

Device events and malfunctions are summarized for the THS 2.2 Menthol arm in [Table 136](#) for the post-randomization period.

**Table 136 Summary of THS 2.2 Menthol Device Events and Malfunctions (THS 2.2 Menthol Study Arm) – Post-Randomization Period**

	THS m2.2 (N=80)	
	n (%)	Events
Number (%) subjects with any device events and malfunctions	55 (68.8%)	149
Is not related to adverse event	55 (68.8%)	149
Major	55 (68.8%)	149
Device inoperable	47 (58.8%)	94
No information	16 (20.0%)	25
Charging issue	9 (11.3%)	12
Device handling issue	3 (3.8%)	4
Break	2 (2.5%)	3
Device difficult to setup or prepare	3 (3.8%)	3
Burn of device or device component	1 (1.3%)	1
Component falling	1 (1.3%)	1
Device issue	1 (1.3%)	1
Electrical issue	1 (1.3%)	1
Failure to power-up	1 (1.3%)	1
Material fragmentation	1 (1.3%)	1
Mechanical issue	1 (1.3%)	1
Out-of-box failure	1 (1.3%)	1

Abbreviations: N = number of subjects randomized; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Percentages were calculated using the N in the column headers.

Data Source: [Appendix 15, Table 15.2.6.15](#).

During THS 2.2 Menthol use in the study, 55 subjects reported a total of 149 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: device inoperable.

## 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

#### 12.2.1.1 Deaths

No deaths occurred in this study.



### 12.2.1.2 Other Serious Adverse Events

Two SAEs were reported by Subject 1119 who was enrolled but not randomized. A brief narrative is presented in [Section 12.2.2](#).

### 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](#).

There were no AEs leading to study discontinuation in any randomized subject. In the pre-randomization period, 2 subjects who were enrolled but not randomized experienced AEs leading to study discontinuation. Subject 2205 experienced an AE of procedural complication, which was an episode of syncope caused by the spirometry assessments. Product use was stopped and the subject was discontinued from the study.

Subject 1233 experienced an AE of syncope. Product use was interrupted and the subject was discontinued from the study.

### 12.2.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Serious AEs of diabetic ketoacidosis and sinusitis were reported by Subject 1119 who was enrolled but not randomized; the subject completed their THS 2.2 Menthol product test on Day -2. The SAEs of diabetic ketoacidosis and sinusitis were first reported on Day -1, were severe in intensity, and not considered to be related to IP use or study procedures. The subject was known to have an ongoing medical history of type 2 diabetes from 2008 ([Appendix 15, Listing 15.3.1.9](#)). The SAE of diabetic ketoacidosis was considered to have resolved after 3 days, while the SAE of sinusitis resolved after 11 days following treatment with concomitant medication. The subject also reported mild AEs of emesis, headache, and nausea, beginning on Day -1 also. The AEs of emesis and nausea resolved on the same day, while the AE of headache resolved 11 days later. None of these AEs were assessed as related to IP use or study procedures.

### 12.2.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Not applicable.



## 12.3 Clinical Laboratory Evaluation

### 12.3.1 Clinical Chemistry

Clinical chemistry data are presented by subject in [Appendix 15, Listing 15.3.6.6](#) including individual changes and shifts from baseline (Day 0) to Days 6, 30, 60, and 91, 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](#) including summaries of low, normal, high, and abnormal CS results.

A total of 12 results from 3 subjects (1.9%), which included 10 results from 1 subject (Subject 2065), which were deemed to be CS by the Principal Investigator were reported for the clinical chemistry values during the study. All results 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 proportion of normal values was 54.5%, which was observed for glucose on Day 0). In general, mean changes from baseline in clinical chemistry parameters were small and comparable between study arms.

Shifts in clinical chemistry parameters in which  $\geq 2$  subjects in any study arm had a shift from normal to low included AST, bilirubin, cholesterol, and LDL-C. Normal to low shifts for AST, cholesterol, and LDL-C were more numerous in the THS 2.2 Menthol arm compared to the mCC and SA study arms.

Shifts from baseline in which  $\geq 2$  subjects in any study arm had a shift from normal to high included cholesterol, AST, ALT, GGT, creatinine, TG, glucose, bilirubin, and LDL-C.

The majority of clinical chemistry variables were normal or classified as grade 1 (mild) on the toxicity grading. Clinical chemistry variables classified as grade 2 (moderate) or grade 3 (severe) on the toxicity grading after the time of product test at Admission were observed in 8 subjects in the THS 2.2 Menthol arm, 7 subjects in the mCC arm, and 4 subjects in the SA arm. The majority of these results were for elevated TG, cholesterol, or potassium and were classed as not CS. Blood triglycerides increased was reported as an AE by 2 subjects in the Confinement Period (1 subject in the THS 2.2 Menthol arm and 1 subject in the SA arm) and 5 subjects in the Ambulatory Period (1 subject in the THS 2.2 Menthol arm, 3 subjects in the mCC arm, and 1 subject in the SA arm). Blood cholesterol increased was not reported as an AE in the Confinement Period and by 1 subject in the SA arm in the Ambulatory Period. Blood potassium increased was reported as an AE by 1 subject in the mCC arm in the Confinement Period and 2 subjects in the THS 2.2 Menthol arm in the Ambulatory Period.





The following subjects had clinical chemistry variables classified as grade 2 (moderate) or grade 3 (severe) on the toxicity grading after the time of product test at Admission which were classed as CS:

- Subject 1209 (THS 2.2 Menthol arm): TG of 438 mg/dL (grade 2, CS) on Day 0, 430 mg/dL (grade 2, NCS) on Day 6/Discharge Confinement, 457 mg/dL (grade 2, NCS) on Day 30, 384 mg/dL (grade 2, NCS) on Day 60, and 397 mg/dL (grade 2, NCS) on Day 91/Discharge Ambulatory.
- Subject 2065 (THS 2.2 Menthol arm): bilirubin of 2.3 mg/dL (grade 2, CS) on Day 60 and 2.2 mg/dL (grade 2, CS) on Day 91/Discharge Ambulatory. GGT of 187 IU/L at Screening (grade 2, NCS), 126 IU/L (grade 2, NCS) on Day 0, 103 IU/L (grade 1, NCS) on Day 6/Discharge Confinement, 93 IU/L (grade 1, NCS) on Day 30, 434 IU/L (grade 3, CS) on Day 60, 307 IU/L (grade 3, NCS) at an unscheduled assessment on Day 65, 812 IU/L (grade 3, CS) on Day 91/Discharge Ambulatory, and 675 IU/L at an unscheduled assessment on Day 94. AST of 109 IU/L (grade 2, NCS) on Day 60, 33 IU/L (normal) at an unscheduled assessment on Day 65, 173 IU/L (grade 2, CS) on Day 91/Discharge Ambulatory, and 65 IU/L (grade 1, CS) at an unscheduled assessment on Day 94.

### 12.3.2 Hematology

Hematology data are presented by subject in [Appendix 15, Listing 15.3.6.7](#) including individual changes and shifts from baseline (Day 0) to Days 6, 30, 60, and 91, 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](#) including summaries of low, normal, high, and abnormal CS results.

Only 1 result from 1 subject (2.4%) which was deemed to be CS by the Principal Investigator was reported for the hematology values during the study and was reported on Day 30. The majority of subjects in all study arms had normal hematology values at each time point (the lowest proportion of normal values was 71.3%, which was observed for mean corpuscular volume on Day 60). In general, mean changes from baseline in hematology parameters were small and comparable between study arms.

Shifts in hematology parameters in which  $\geq 2$  subjects in any study arm had a shift from normal to low included erythrocytes, hemoglobin, erythrocyte mean corpuscular hemoglobin concentration, erythrocyte mean corpuscular hemoglobin, neutrophils, hematocrit, platelets, total WBC (leukocytes), and monocytes.

Shifts from baseline in which  $\geq 2$  subjects in any study arm had a shift from normal to high included erythrocyte mean corpuscular volume, hematocrit, platelets, lymphocytes, monocytes, and total WBC (leukocytes).





The majority of hematology variables were normal or classified as grade 1 (mild) on the toxicity grading. However, there were 55 values classified as grade 2 (moderate) on the toxicity grading, and 5 values classified as grade 3 (severe) on the toxicity grading.

Those classified as grade 2 included decreased hemoglobin, decreased neutrophils, lymphocytes increased, and total WBC (leukocytes) increased. Those that were classified as grade 3 were all decreased hemoglobin values, with 3 values reported for the THS 2.2 Menthol arm (2 on Day 60 and 1 on Day 91/Discharge Ambulatory), 1 value reported for the mCC arm on Day 30, and 1 value reported for the SA arm on Day 60.

As presented in [Table 132](#), 9 subjects had AEs for hematology parameters in the Confinement Period and 27 subjects had AEs for hematology parameters in the Ambulatory Period. In the Confinement Period, 5 subjects had AEs of hemoglobin decreased (3 in the THS 2.2 Menthol arm and 2 in the SA arm), 3 subjects had AEs of lymphocyte count increased (2 in the THS 2.2 Menthol arm and 1 in the mCC arm), and 1 subject had an AE of neutrophil count decreased (THS 2.2 Menthol arm). In the Ambulatory Period, 17 subjects had AEs of hemoglobin decreased (8 in the THS 2.2 Menthol arm, 4 in the mCC arm, and 5 in the SA arm), 7 subjects had AEs of lymphocyte count increased (5 in the THS 2.2 Menthol arm, 1 in the mCC arm, and 1 in the SA arm), and 3 subjects had AEs of neutrophil count decreased (all THS 2.2 Menthol arm).

The majority of post-randomization AEs for hematology parameters were considered moderate in severity and all AEs were considered not related to the IP and study procedures.

### 12.3.3 Urinalysis

Urinalysis data are presented by subject in [Appendix 15, Listing 15.3.6.8](#) including individual changes and shifts from baseline (Day 0) to Days 6, 30, 60, and 91, 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](#) including summaries of low, normal, high, and abnormal CS results.

There were no results which were deemed to be CS by the Principal Investigator for the urinalysis values during the study. The majority of subjects in all study arms had normal urinalysis values during the study (the lowest proportion of normal values was 59.4%, 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 parameters, there were 26 values classified as grade 1 and 3 classified as grade 2. All grade 1 and grade 2 protein in urine values were classed as



NCS. Eight grade 1 values were reported in the THS 2.2 Menthol arm, 7 grade 1 values were reported in the mCC arm, and 11 grade 1 values were reported in the mCC arm. The greatest number of grade 1 values for this parameter was present on Day 6/Discharge Confinement (10 values). The 3 grade 2 values corresponded to 2 AEs reported during the study in the SA arm:

- Subject 1143 had an AE of protein urine which was first observed on Day 6/Discharge Confinement (grade 2) and was present on Day 30 also (grade 2). The AE was considered resolved on Day 35 following a negative protein assessment on Day 35. The AE lasted for 30 days, was considered to be mild in severity, and not related to the IP or study procedures.
- Subject 2209 had an AE of proteinuria reported on Day 31 (grade 2), which was considered resolved at following urinalysis Day 60 assessment (Day 61). The AE was considered to be moderate in severity and not related to the IP or study procedures.

Two values from 2 subjects for glucose in urine were classified as grade 3, considered not to be CS, and corresponded to 2 AEs reported during the study:

- Subject 2316 of the THS 2.2 Menthol arm had an AE of glycosuria first reported on Day 91/Discharge Ambulatory, which was ongoing at the EOS. It was considered to be severe in severity and not related to the IP or study procedures.
- Subject 2079 of the SA arm had an AE of glycosuria first reported on Day 91/Discharge Ambulatory, which was ongoing at the EOS. It was considered to be moderate 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 15.3.6.9](#) including individual changes from baseline.

Vital signs data are summarized for the Safety Population in [Appendix 15, Table 15.2.6.20](#) including summaries of changes from baseline at each assessment time point.

In general, vital signs results were comparable between study arms and any mean changes from baseline were small and comparable between study arms.

Syncope was reported as an AE on Day 0 by 4 subjects; 3 subjects in the THS 2.2 Menthol arm (Subjects 1060, 1144, and 1177) and 1 subject who was enrolled but not



randomized (Subject 1233, see [Section 12.2.1.3](#)). Vital sign assessments on Day 0 were normal for all 4 subjects and the AEs were assessed as being related to study procedures.

Presyncope was reported as an AE by 3 subjects; 2 subjects in the THS 2.2 Menthol arm (Subjects 1281 on Day 0 and Subject 1297 on Day 2) and 1 subject in the SA arm on Day 0 (Subject 1219). Vital sign assessments were normal for all 3 subjects on the day of the AE and Subjects 1281 and 1291 AEs were assessed as being related to study procedures.

#### 12.4.2 Physical Examinations

Physical examination findings (including height, weight, and BMI) are presented by subject in [Appendix 15, Listing 15.3.6.12](#) and summarized for the Safety Population in [Appendix 15, Table 15.2.6.23](#). Weight and BMI data are summarized for the Safety Population in [Appendix 15, Table 15.2.6.24](#).

There were no CS physical examination findings recorded during the study. 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 15.3.6.10](#) 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 a finding that had shifted from normal to abnormal compared with baseline that was considered to be CS.

#### 12.4.4 Full Lung Function Assessments

Full lung function data are presented by subject in [Appendix 15, Listing 15.3.6.11](#).

Full lung function results for the Safety Population are summarized in [Appendix 15, Figure 15.1.2.30](#) and [Appendix 15, Table 15.2.6.22](#) including summaries of changes from baseline to Day 6/Discharge Confinement and to Day 91/Discharge Ambulatory.

In all study arms, all subjects at Screening had post-bronchodilator  $FEV_1/FVC \geq 0.54$ , post-bronchodilator  $FEV_1 \geq 62\%$  predicted, and post-bronchodilator  $FVC \geq 64\%$  predicted.



Abnormal CS results were observed for a number of subjects during the study:

- Two subjects overall (1.3%) on Day 0 without bronchodilator; 1 subject in the THS 2.2 Menthol arm (1.3%) and 1 subject in the mCC arm (2.4%)
- Five subjects overall (3.3%) on Day 6/Discharge Confinement without bronchodilator; 3 subjects in the THS 2.2 Menthol arm (3.8%), 1 subject in the mCC arm (2.5%), and 1 subject in the SA arm (3.0%)
- One subject (0.7%) on Day 6/Discharge Confinement with bronchodilator in the THS 2.2 Menthol arm (1.3%)
- Three subjects (2.2%) on Day 91/Discharge Ambulatory without bronchodilator; 2 subjects in the THS 2.2 Menthol arm (2.7%) and 1 subject in the SA arm (3.2%)
- One subject (0.7%) on Day 91/Discharge Ambulatory with bronchodilator in the THS 2.2 Menthol arm (1.4%)

Lung function results and changes from baseline during the randomization period are summarized in [Table 137](#).





**Table 137 Summary of Full Lung Function Results and Changes from Baseline – Safety Population**

Parameter (units) Study Day	THS m2.2		mCC		SA	
	Arithmetic mean	Change	Arithmetic mean	Change	Arithmetic mean	Change
DLCO (mL/min/mmHg)						
n	76		40		33	
Baseline	23.290		24.379		23.118	
n	77	75	40	40	33	31
Day 6	23.453	0.171	23.567	-0.813	23.005	0.008
n	71	70	34	34	31	29
Day 91	23.323	0.470	24.994	-0.019	22.558	-0.034
KCO (mmol/min/kPa/L)						
n	76		40		33	
Baseline	1.376		1.344		1.325	
n	77	75	40	40	33	31
Day 6	1.373	-0.001	1.322	-0.023	1.326	-0.022
n	71	70	34	34	30	28
Day 91	1.408	0.040	1.346	-0.021	1.327	0.013
FEV <sub>1</sub> (L) with bronchodilator						
n	79		41		39	
Baseline	3.386		3.633		3.379	
n	78	78	40	40	33	33
Day 6	3.388	0.008	3.624	-0.048	3.414	0.116
n	74	74	34	34	31	31
Day 91	3.250	-0.109	3.587	-0.101	3.175	-0.089
FEV <sub>1</sub> (% pred) with bronchodilator						
n	79		41		39	
Baseline	93.4		96.3		92.9	
n	78	78	40	40	33	33
Day 6	93.2	-0.2	95.1	-1.5	95.6	3.2
n	74	74	34	34	31	31
Day 91	89.1	-4.2	92.8	-3.5	88.8	-3.1
FVC (L) with bronchodilator						
n	79		41		39	
Baseline	4.271		4.630		4.304	
n	78	78	40	40	33	33



**Table 137 Summary of Full Lung Function Results and Changes from Baseline – Safety Population (continued)**

Parameter (units) Study Day	THS m2.2		mCC		SA	
	Arithmetic mean	Change	Arithmetic mean	Change	Arithmetic mean	Change
Day 6	4.281	0.015	4.632	-0.044	4.243	0.078
n	74	74	34	34	31	31
Day 91	4.129	-0.091	4.581	-0.110	4.021	-0.107
FVC (% pred) with bronchodilator						
n	79		41		39	
Baseline	94.6		99.8		95.2	
n	78	78	40	40	33	33
Day 6	94.9	0.3	98.6	-1.6	95.8	1.9
n	74	74	34	34	31	31
Day 91	91.5	-2.6	96.7	-2.8	91.3	-2.2
FEV <sub>1</sub> /FVC (ratio)						
n	78		40		35	
Baseline	0.796		0.787		0.792	
n	78	78	40	40	33	33
Day 6	0.791	-0.005	0.784	-0.003	0.804	0.013
n	74	74	34	34	31	31
Day 91	0.789	-0.010	0.785	-0.003	0.791	0.000
MEF 25-75 (L/s) with bronchodilator						
n	79		41		39	
Baseline	3.231		3.344		3.153	
n	78	78	40	40	33	33
Day 6	3.268	0.049	3.380	-0.010	3.302	0.160
n	73	73	34	34	31	31
Day 91	4.753	1.491	5.592	2.211	3.073	-0.035
TLC (L)						
n	78		40		35	



**Table 137 Summary of Full Lung Function Results and Changes from Baseline – Safety Population (continued)**

Parameter (units) Study Day	THS m2.2		mCC		SA	
	Arithmetic		Arithmetic		Arithmetic	
	mean	Change	mean	Change	mean	Change
Baseline	5.944		6.142		5.908	
n	78	78	40	40	33	33
Day 6	6.007	0.062	6.227	0.085	6.066	0.194
n	74	74	34	34	31	31
Day 91	5.789	-0.095	6.018	-0.241	5.592	-0.265
FRV (L)						
n	78		40		35	
Baseline	3.083		3.158		2.951	
n	78	78	40	40	33	33
Day 6	2.919	-0.164	3.165	0.007	3.097	0.153
n	74	74	34	34	31	31
Day 91	2.801	-0.285	3.031	-0.171	2.823	-0.124
IC (L)						
n	78		40		35	
Baseline	2.861		2.984		2.957	
n	78	78	40	40	33	33
Day 6	3.088	0.227	3.062	0.078	2.968	0.042
n	74	74	34	34	31	31
Day 91	2.989	0.190	2.987	-0.071	2.769	-0.141
VC (L)						
n	78		40		35	
Baseline	4.335		4.732		4.272	
n	78	78	40	40	33	33
Day 6	4.385	0.051	4.679	-0.053	4.299	0.081
n	73	73	34	34	31	31
Day 91	4.277	-0.021	4.584	-0.170	4.096	-0.087

Abbreviations: CO = carbon monoxide; DLCO = diffusion capacity for lung CO; FEV<sub>1</sub> = forced expiratory volume in 1 second; FRV = forced residual volume; FVC = forced vital capacity; IC = inspiratory capacity; KCO = rate constant of CO; mCC = Menthol conventional cigarette; MEF = mid expiratory flow; N = number of subjects in arm; n = number of subjects; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol; TLC = total lung capacity; VC = vital capacity.

Data Source: [Appendix 15, Tables 15.2.6.22](#).

There was no apparent change in gas transfer parameters (DLCO and KCO) or lung volume (FRV, VC, TLC, and IC). There was no apparent change in spirometry parameters (FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC), with the exception of MEF 25-75, as changes



from baseline tended to be small or comparable between study arms. MEF 25-75 increased in the THS 2.2 Menthol and mCC arms between baseline and Day 91/Discharge Ambulatory while MEF 25-75 remained stable in the SA arm.

#### 12.4.5 Assessment of Cough

Subject listings for the assessment of cough are presented by subject in [Appendix 15, Listing 15.3.6.23](#).

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](#).

The number of subjects who experienced a cough in the pre-randomization period was low (21.8%) and evenly distributed between study arms (17.1% to 23.1%), with the most common intensity being very mild. Two of the enrolled but not randomized subjects (40.0%) also experienced a cough. One subject in the THS 2.2 arm reported a severe cough on Day 0.

Overall, the number of subjects who experienced a cough during the randomization period was moderately high (74 subjects, 46.3%). The incidence of cough was similar between the THS 2.2 Menthol, mCC, and SA study arms (47.5%, 43.9%, and 46.2%, respectively). Cough intensity was comparable between the THS 2.2 Menthol, mCC, and SA arms, with the most commonly reported cough intensities being very mild (34.2%, 33.3%, and 27.8%, respectively) and mild (34.2%, 44.4%, and 50.0%, respectively). A severe cough was reported by Subject 1104 in the mCC arm on Day 1, and very severe coughs were reported on Day 6/Discharge Confinement by Subject 2140 in the THS 2.2 Menthol arm and Subject 2029 in the SA arm. Subject 2140 had previously reported a very mild cough on Day 2 and Subject 2029 had previously reported very mild, mild, and moderate intensity coughs on Days 2, 4, and 5, respectively.

Cough frequency during the randomization period was comparable between the THS 2.2 Menthol, mCC, and SA arms, with the most commonly reported cough frequencies being rarely (36.8%, 27.8%, and 27.8%, respectively) and sometimes (36.8%, 38.9%, and 44.4%, respectively). Three subjects in the THS 2.2 Menthol arm reported almost always having a cough during the randomization period. Subject 1028 reported almost always for cough frequency on Day 3, but rarely or sometimes for Days 0, 1, 2, 4, 5, 6, and 30. By Day 60, Subject 1028 was not experiencing any coughing. Subject 1252 reported almost always for cough frequency on Day 5, and either sometimes or fairly often for Days 0 to 4. On Days 30 and 60 Subject 1252 did not experience any coughing. Subject 2274



reported almost always for cough frequency on Day 3, and often for cough frequency on Days 2, 4, 6, and 30. By Day 60, cough frequency had reduced to fairly often.

The majority of subjects who experienced cough reported either no sputum or a moderate amount of sputum, with the exception of 3 subjects (post-randomization). In the THS 2.2 Menthol, mCC, and SA arms, no sputum was reported by 50.0%, 50.0%, and 38.9% of subjects who experienced a cough, respectively, while a moderate amount of sputum was reported by 44.7%, 38.9%, and 61.1% of subjects who experienced a cough. Subject 2274 in the THS 2.2 Menthol arm reported a very large amount of sputum on Days 2, 6, 60, and 90; Subject 2138 in the mCC arm reported a larger amount of sputum on Day 60; and Subject 1251 in the THS 2.2 Menthol arm reported a larger amount of sputum on Day 90.

Over the course of the study, the percentage of subjects who reported a cough decreased from that observed during the Confinement Period (Days 1 to 6) to that observed in the Ambulatory Period (Days 30, 60, and 90) in the THS 2.2 Menthol and SA arms ([Appendix 15, Table 15.2.6.25.1](#)). In the THS 2.2 Menthol arm, the percentage of subjects was 18.8% to 22.5% for Days 1 to 6 and this decreased to 10.0% on Day 30, 2.5% on Day 60, and 8.8% on Day 90. Decrease in the SA arm was more marked, with 17.9% to 30.8% of subjects reporting a cough for Days 1 to 6, decreasing to 2.6% (1 subject) on Day 30 and no subjects on Days 60 and 90. The percentage of subjects who reported a cough did decrease in the mCC arm from the Confinement Period to the Ambulatory Period, although not by as much as the other 2 study arms. In the Confinement Period, 17.1% to 26.8% of subjects reported a cough, and this decreased to 9.8% on Days 30 and 60, and 12.2% on Day 90.

Analysis of the cough impact scale data (VAS) showed that mean VAS was similar during the Confinement Period for the THS 2.2 Menthol and mCC study arms, with values fluctuating between 19.2 and 32.3 for the THS 2.2 Menthol arm and 16.4 and 30.0 for the mCC arm. In the Ambulatory Period, mean VAS scores were comparable between the THS 2.2 Menthol and mCC arms on Day 30 (24.8 and 21.3, respectively), but VAS scores were lower in the THS 2.2 Menthol study arm on Days 60 and 90 (29.0 and 21.8) compared to the mCC arm (45.8 and 45.3). In the SA study arm, mean VAS scores increased from Day 1 (13.9) to Day 6/Discharge Confinement (29.4). In the Ambulatory Period, only 1 subject reported a cough on Day 30 (VAS score of 4.0) and no subjects reported a cough on Days 60 and 90.

## 12.5 Safety Conclusions

There were no SAEs reported by any randomized subject in this study and no randomized subjects were discontinued due to an AE. Prior to randomization, 4 subjects were discontinued from the study, of which 2 subjects were discontinued due to an AE. One subject reported 2 SAEs which were not related to the IP or study procedures and led to the discontinuation of the subject from the study.





Overall, there were 195 AEs reported post-randomization by 95 of the 160 subjects (59.4%) in the Safety Population, most of which were mild or moderate in severity. Twelve severe AEs were reported during the Ambulatory Period, all of which were due to abnormal clinical laboratory findings and were unrelated to IP or study procedures.

The incidence of post-randomization AEs was comparable in the THS 2.2 Menthol arm (52 of 80 subjects [65.0%]) and the SA arm (23 of 39 subjects [59.0%]), and slightly lower in the mCC arm (20 of 41 subjects [48.8%]). Similarly, the frequency of AEs was comparable in the THS 2.2 Menthol arm (114 AEs from 80 subjects) and the SA arm (49 AEs from 39 subjects), and slightly lower in the mCC arm (32 AEs from 41 subjects).

There were 6 AEs reported which were considered to be related to the IP during the Confinement Period, and 2 AEs which were considered to be related in the Ambulatory Period. Seven AEs were considered as related to study procedures, with 6 occurring during the Confinement Period and 1 during the Ambulatory Period.

Overall, the most frequent AEs reported post-randomization by SOC were Investigations, which were experienced by 27/80 subjects (33.8%) in the THS 2.2 Menthol arm, 11/41 subjects (26.8%) in the mCC arm, and 12/39 subjects (30.8%) in the SA arm.

The most frequent AEs by PT reported were decreased hemoglobin, increased lymphocyte count, upper respiratory tract infection, and headache with the majority of incidences occurring for these PTs during the Ambulatory Period. Throughout the study, 11/80 subjects (13.8%) in the THS 2.2 Menthol arm, 4/41 subjects (9.8%) in the mCC arm, and 6/39 subjects (15.4%) in the SA arm experienced decreased hemoglobin (haemoglobin decreased). The proportion of subjects who experienced increased lymphocyte count, upper respiratory tract infection, and headache was <10% of the subjects in each study arm.

Overall, 55 subjects in the THS 2.2 Menthol arm (68.8%) reported a total of 149 major device events or malfunctions; 27 subjects (33.8%) during the Confinement Period and 46 subjects (57.5%) during the Ambulatory Period. None of these events led to an AE.

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

There were no safety relevant changes in lung function in any study arm during the course of the study. There were no notable differences on Day 6/Discharge Confinement and Day 91/Discharge Ambulatory in gas transfer parameters (DLCO and KCO), lung volume parameters (FRV, TLC, and IC), or spirometry parameters (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and MEF 25-75) between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. On Day 91/Discharge Ambulatory, VC was 0.10 L higher in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC (95% CI: 0.00, 0.21).





## 13 DISCUSSION AND OVERALL CONCLUSIONS

### 13.1 Discussion

This study was designed to demonstrate the reduction in exposure to selected HPHCs achievable in a confined setting, and sustainable in a 3-month ambulatory setting, when switching exclusively from mCC to THS 2.2 Menthol use, compared to subjects who continued to smoke mCC, over 3 months. Smokers who remained abstinent from smoking were used as a benchmark to provide context to the exposure reductions.

The THS 2.2 Menthol 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 optimal exposure reduction to HPHCs in subjects using predominantly THS 2.2 Menthol; the PP Set Population included all subjects randomized, with no major protocol deviations and who were compliant to their allocated product (not more than 2 CC on any day, and not more than 0.5 CC 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 the product subjects had been allocated to (THS 2.2 Menthol or mCC) or continuous abstinence from smoking in the SA arm followed by an Ambulatory Period of 86 days, 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 in a non-residential setting. The Confinement Period investigated the maximum possible exposure reduction to selected HPHCs, whereas, the Ambulatory Period investigated if the exposure reduction to selected HPHCs observed during the Confinement Period was sustained in a less controlled, more real-life setting where confounding factors such as diet and passive smoking are known to influence levels of some BoExp.

Furthermore, this study evaluated the adaptation to and acceptance of THS 2.2 Menthol as a substitute to 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 (39). 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 sustained reductions in the corresponding BoExp levels (except S-BMA and NEQ) were observed throughout the entire Exposure Period with reductions of 51%



to 96% and 34% to 86% on Day 5 and Day 90, respectively, in subjects who switched from mCC to THS 2.2 Menthol compared to those who continued smoking mCC. The reductions observed are a result of the THS 2.2 Menthol heat not burn product design, by which combustion is minimized or eliminated and thus suggests that THS 2.2 Menthol reduces the exposure to HPHCs found in cigarette smoke beyond the toxicants measured in this study. These insights are consistent with the results of the analyses on the THS 2.2 Menthol aerosol chemistry where HPHCs were found to be reduced by at least 90% when compared to a reference cigarette (5).

Overall, the magnitude of HPHCs exposure reduction was comparable between the Confinement and Ambulatory Periods, although less pronounced in the Ambulatory Period for some HPHCs assessed. Potential confounding factors associated with the “real-life” conditions of the Ambulatory Period 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, as THS 2.2 Menthol consumption was comparable to mCC use during the Ambulatory Period. In addition, the occasional use of CC, which was allowed in the THS 2.2 and SA arms, could add to the explanation.

The reductions observed in the levels of o-tol, Total NNAL, and CEMA in the Ambulatory Period were greater than that observed in the Confinement Period, with reductions of 51% on Day 5 and 56% on Day 90 for o-tol, reductions of 56% on Day 5 and 73% on Day 90 for Total NNAL, and reductions of 82% on Day 5 and 85% on Day 90 for CEMA observed in the THS 2.2 Menthol arm compared to the mCC arm. In contrast to the other BoExp, which exhibit a half-life of a few hours to approximately 1 to 2 days, the elimination half-life for Total NNAL is 10 to 18 days (10). In addition, for CEMA, in contrast to the paper which reported an estimated elimination half-life of 7 hours (40), preliminary analysis derived from a PMI study (ClinicalTrials.gov: NCT01465880) showed the estimated half-life was approximately 17 to 18 hours or even longer (data on file). As a consequence, the time-to-maximum elimination, expected to be achieved after a 4- to 5-fold elimination half-life, may exceed the duration of the Confinement Period and therefore, potentially explain the greater Total NNAL and CEMA reduction observed during the Ambulatory Period.

The S-BMA (BoExp to toluene) levels were similar across the 3 arms in contrast to the differentiation observed in other BoExps. Although S-BMA is a suitable BoExp to toluene in environmental and occupational studies (41), its suitability to discriminate between smokers and non-smokers is questionable. Various studies have reported overlapping ranges in S-BMA levels with only subtle increases observed between smokers and non-smokers (41-43), a finding which is in agreement with the results 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" (44). The 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 higher levels observed for Total NNN and 3-HPMA at both, Day 5 and Day 90, and for o-toluidine, and B[a]P on Day 5 only, compared to SA might be best explained by the nature of the product and the residual levels of the corresponding HPHCs in the aerosol of THS 2.2 Menthol as evaluated by the smoke chemistry. For 3-HPMA and o-toluidine, exposure through sources other than THS 2.2 Menthol use, such as food or other environmental exposure may have played a role. Furthermore, endogenous formation of small amounts of acrolein and its metabolites during the catabolism of various amino acids and polyamines and metabolic variability may have added on the 3-HPMA rate and amount of excretion. For 3-HPMA, the Day 5 reduction of 54% observed following the use of THS 2.2 Menthol was smaller than the expected 70% reduction (see [Section 9.7.5](#)). However, the THS 2.2 Menthol versus SA ratio was 183% on Day 5, close to the anticipated value of 170%, thus suggesting that the reduction in subjects switching from mCC to SA was correspondingly smaller than the SA effect observed in previous studies (with LS geometric means of 278.13 ng/mg creat for the THS 2.2 Menthol study arm and 152.05 ng/mg creat for the SA study arm). Similar to 3-HPMA, the levels of Total NNN on Day 5 showed differences between the THS 2.2 Menthol and SA arm (geometric LS mean of THS 2.2 Menthol versus SA: 678.32%); however, the numerical values for both the THS 2.2 Menthol and SA arms were within a close range of each other (0.91 and 0.13 pg/mg creat, respectively) and at very low levels, therefore, the majority of the decrease of the SA arms was preserved in the THS 2.2 Menthol arm.

Baseline COHb levels were in agreement with the levels found in smokers (Institute of Medicine reports ranges of 3.4% to 7.1% (44) 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 61.86% relative to mCC after 5 days of product use, and were sustained (53.24%) 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 2.66% and 2.84%, 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 (45). Similarly the WHO environmental health criteria 213 on CP states that a COHb level of 2.5% should not be exceeded so as to prevent untoward hypoxic effects on the non-smoking population with coronary artery diseases (46). In the THS 2.2 Menthol arm of this study, the recommended levels of the Agency for Toxic Substances and Disease and the WHO are slightly exceeded, but this was unlikely to have resulted from THS 2.2 Menthol use, as levels were comparable to THS 2.2 Menthol in the SA arm. Environmental exposure to CO might play a role and best explain this observation.



Differences in laboratory analysis methods used to measure COHb compared to the studies reported in the literature may have played a role.

There was sustained reduction in levels of urinary mutagenicity as assessed by the Ames test in the THS 2.2 Menthol users throughout the study (72% reduction from baseline following 5 days of THS 2.2 product use and 64% reduction from baseline following 90 days of product use) compared to mCC users (47% increase from baseline following 5 days and 22% increase from baseline following 90 days). These are likely a direct effect of exposure reduction to HPHCs when switching from mCC to THS 2.2 Menthol as urine mutagenicity test reflects the mutagenic load in the urine of subjects. A decrease in levels of urinary mutagenicity was apparent in both the THS 2.2 Menthol and SA arms during the entire Exposure Period (both the Confinement and Ambulatory Periods) a finding consistent with markedly lower mutagenic response of THS 2.2 Menthol relative to reference cigarette results from pre-clinical studies (5). The considerable variability of results observed in this study could be explained by the high test sensitivity to dietary mutagens, and the complexity of this cellular test. However, the results observed still indicate an overall lower level of mutagenic compounds in the urine of users of THS 2.2 Menthol compared to mCC smokers (47).

Overall, the study results demonstrate the use of THS 2.2 Menthol to significantly reduce exposure to HPHCs close to levels reported in the literature after 90 days of smoking abstinence in the PP Set Population (48). This study demonstrated that despite the various confounding factors which may influence the levels of exposure to selected HPHCs, the reduction in exposure achieved at the end of the Confinement Period was sustained at the end of the Ambulatory Period.

### **Product Use Assessment**

Overall, the average daily THS Menthol Tobacco Stick consumption increased by approximately 16.5% in the THS 2.2 Menthol arm between baseline and the end of the Exposure Period. There was an initial increase in consumption from baseline to Day 5 to Day 30 and only limited change to the end of the Ambulatory Period. In the mCC arm, the number of mCC smoked daily increased through the course of the study, with a slightly higher mCC use at Day 90 compared to baseline. A high level of compliance was observed in this study, with 78.8% predominant or primary users (over 70%) in the THS 2.2 Menthol arm during the Ambulatory Period, while 12.5% reported dual-use. The initial increase of product consumption was likely driven by an initial marked drop of nicotine levels from baseline to Day 2 before nicotine levels reached levels close to baseline on Day 30, with levels comparable to subjects who continued to smoke mCC, and fluctuated in a range comparable to mCC thereafter. Levels of cotinine followed a similar trend. 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 increase from baseline on total puff volume (a measure to estimate the subject's total exposure to THS at the mouth level) of approximately 37% on Day 1 and 49% on Day 4. The total puff volume further fluctuated throughout the Ambulatory Period with levels higher to what was observed in the mCC arm on Day 90 (766 mL). The adaptation of total puff volume over time was mainly driven by changes in average puff volume, average puff duration, and average inter puff interval.

The changes in the HST parameters combined with the changes in product use and nicotine exposure are likely related to the adaptation process following the initial days after switching from mCC to THS 2.2 Menthol, to achieve the levels of nicotine desired.

### **Subjective Effects**

This study included endpoints to assess the overall satisfaction and acceptance by subjects of THS 2.2 Menthol as a substitute for mCC.

The mean urge-to-smoke scores, as assessed by the QSU-brief questionnaire were similar, stable, and comparable to baseline throughout the entire Exposure Period for THS 2.2 Menthol and mCC arms. In contrast, mean urge-to-smoke scores in the SA arm had a sharp increase from baseline on Day 1 then decreased, reaching similar mean values to that observed in the THS 2.2 Menthol and mCC arms by Day 5. From Day 5 to Day 30, the mean urge-to-smoke score in the SA arm decreased further before plateauing from Day 30 to Day 90.

Similar results were observed for withdrawal symptoms scores using the MNWS-R questionnaire, where no apparent difference between subjects who switched to THS 2.2 Menthol and smokers who continued to smoke mCC was shown. By contrast, and as expected, an initial increase from baseline was evident in the SA arm which gradually decreased from Day 1 to Day 5, and was comparable to the scores from the THS 2.2 Menthol and mCC arms.

Furthermore, the MCEQ showed scale marked drops on the first day after switching to THS 2.2 Menthol; whereas mCC values were unchanged during the entire study. A lower THS 2.2 Menthol evaluation in most subscales was noted on all days of Confinement; although, the scores recovered gradually, with scores on Days 30, 60, and 90 close to those achieved for mCC.

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, in concordance with nicotine exposure and product use that subjects successfully adapted over time to the new product and that the THS 2.2 Menthol product provided similar levels of satisfaction and enjoyment to that of mCC.

### **Risk Markers**

The disorders induced by smoking CC are complex as there are multiple causal chains and diseases develop over many years. 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. Consequently, there is no single CRE that, in and of itself, can be considered as a validated surrogate measure for the adverse health effects associated with smoking. 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 would indicate a favorable risk profile against which to assess a candidate MRTP such as THS 2.2 Menthol.

The CREs monitored in this study included markers related to lipid metabolism (HDL-C), inflammation (total WBC [leukocytes] count), endothelial dysfunction (sICAM-1), platelet activation (11-DTX-B2), and oxidative stress (8-epi-PGF<sub>2α</sub>), as all of these play a role in, and contribute to, cardiovascular risk factors and/or are markers of changes in several other smoking-related disease pathways. All these are reported in the literature to be unfavorably affected by smoking, with changes being reversible upon smoking cessation (13, 49, 50).

Other markers such as systolic and diastolic blood pressure, TG, LDL-C, platelet count, fibrinogen, HbA1c, waist circumference, and weight were also assessed to provide overall context and comprehensive information on the cardiovascular risk profile of subjects. Full lung function was also assessed in smokers switching from mCC to THS 2.2 Menthol as an indicator of respiratory disease development.

For the majority of the lung function parameters assessed post-bronchodilator, there were generally no differences between subjects continuing smoking, and subjects switching to THS 2.2 Menthol, nor were there CS differences relative to SA, as expected considering the duration of the study. Changes in lung function require a longer investigational period and a favorable change in FEV<sub>1</sub>% predicted would be expected after a minimum period of 6 to 12 months of smoking cessation (51). However, an increase in VC of 0.10 L at Day 90 in the THS 2.2 Menthol arm relative to mCC arm may indicate promising results towards potential improvements in respiratory function upon THS 2.2 Menthol use compared to mCC in the longer term.



Other favorable changes were observed for sICAM-1 and 8-epi-PGF<sub>2α</sub>, in the THS 2.2 Menthol arm, with levels 11% and 14% lower on Day 90 compared to subjects who continued to smoke mCC, and close to what was observed in the SA arm.

However, the other CREs associated with cardiovascular diseases (11-DTX-B2 levels, TG, HDL-C, and LDL-C, homocysteine, fibrinogen, hs-CRP, systolic and diastolic blood pressure, blood glucose, HbA1c, body weight, and waist circumference) showed no notable differences in either the THS 2.2 Menthol or SA study arms, nor were there notable or marked differences compared to values at baseline. Possible explanations are that favorable changes may require longer periods of switching to THS 2.2 Menthol use, or SA, than the duration of this study allowed; although, literature reports at least 2 weeks for changes in 11-DTX-B2 to be observed (52, 53). Furthermore, the study was not designed to primarily assess these markers, and a larger sample of subjects would be needed to observe favorable changes in some of the CREs; also, natural variability and factors such as age, sex, smoking history, or concomitant medication may add to the explanation of these results leading to the need for further investigation in a larger sample over a longer period of time to better determine these results. Overall, initial favorable changes in some CREs were seen in the THS 2.2 Menthol arm shifting towards the direction of smoking cessation as observed in the SA arm. These results suggested that the exposure reduction achieved with switching to THS 2.2 Menthol may translate into reduced risk of smoking-related disease development with use of THS 2.2 Menthol over time.

### **CYP1A2 and CYP2A6**

The study evaluated the impact of using THS 2.2 Menthol on CYP proteins, i.e., CYP1A2 and CYP2A6.

The CYP1A2 enzymes are mono-oxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines (54). CYP1A2 also catalyzes many of the reactions involved in the metabolism of low therapeutic-index drugs and synthesis of cholesterol, steroids, and other lipids (55). The CYP1A2 expression is induced to a large extent by polycyclic aromatic hydrocarbons (PAH) which are found in cigarette smoke (56).

In this study, CYP1A2 activity in subjects who switched to THS 2.2 Menthol was reduced to similar levels as those observed in subjects who abstained from smoking and are in line with what is reported in the literature following 5 days of SA (11). 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 reduced CYP1A2 activity after THS 2.2 Menthol use and SA.



The ratio of nicotine metabolite, trans-3'-hydroxycotinine, to cotinine in biological fluids is an indicator of CYP2A6 activity which is highly correlated with the rate of nicotine metabolism. In this study, CYP2A6 activity was 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 because the two arms had similar exposure to nicotine. As nicotine itself reduces the rate of its own metabolism by inhibiting CYP2A6 activity (57), 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 (58-60).

### **Safety**

There were no SAEs reported by any randomized subject in this study and no randomized subjects were discontinued due to an AE. The majority of AEs were mild in severity, although 12 severe AEs were reported during the Ambulatory Period, all of which were due to abnormal clinical laboratory findings and were unrelated to IP or study procedures.

The incidence of subjects experiencing post-randomization AEs was comparable in the THS 2.2 Menthol arm and SA arms, and slightly lower in the mCC arm. Similarly, the frequency of AEs was comparable in the THS 2.2 Menthol arm (114 AEs from 80 subjects) and the SA arm (49 AEs from 39 subjects), and slightly lower in the mCC arm (32 AEs from 41 subjects).

### **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 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 to 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. The correlation and concordance found between the concentrations of BoExp to HPHCs in 4-hour and 24-hour urine collection indicate possibility for future studies to minimize the operational burden associated with the 24-hour urine collection while maintaining accurate estimates of excretion of BoExp in urine.

In addition, the number and variety of BoExp assessed was another strength of the 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 advocates 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: (a) being specific to the source of exposure with other sources being minor or non-existent, (b) being 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, (f) covering a broad variety of chemical classes and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential).

The study had good compliance in the THS 2.2 Menthol arm and relatively poor compliance to abstinence from smoking during the Ambulatory Period, with only 7 to 9 out of 41 subjects meeting the criteria for inclusion in the PP Set. The challenge for participants to keep abstinent from smoking for 3 months, together with the incorrect randomization of 5 subjects, as described in [Section 10.2](#), resulted in a limited number of subjects in the PP Set on Day 90. This had the effect of increasing the ratios variability between THS 2.2 Menthol users with those who abstained from smoking, resulting in broad ranges of 95% CI values for each assessed BoExp. Due to the study design, targeting BoExp assessment, the limited timing and sample size to assess CRE results did not allow a conclusive interpretation of the results; although most CREs started to show favorable changes shifting in the direction of SA. In light of the limited number of subjects in the SA arm and the increased variability, the results obtained using the SA arm should be interpreted with caution.

### 13.2 Overall Conclusions

The study demonstrated that switching from mCC smoking to THS 2.2 Menthol use resulted in substantial reductions in exposure to assessed HPHCs, with the majority of the reduction achieved after 5 days in Confinement and sustained throughout the 86 days of the Ambulatory Period of the study, while maintaining comparable levels of nicotine. The kinetics of the reductions observed for the majority of BoExp levels in the THS 2.2 Menthol arm were similar to those observed in the SA arm, in both the timing and magnitude of the reductions.

Exposure to nicotine decreased from baseline to Day 2 before rising to levels similar to baseline on Day 30 and was comparable to levels observed in subjects who continued to smoke mCC. The levels of nicotine observed for THS 2.2 Menthol and mCC declined slightly afterwards with comparable levels for both the THS 2.2 Menthol and mCC arms on Day 90.

Most likely driven by the initial decrease in nicotine exposure, product use consumption initially increased in average unit consumption from baseline 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 Exposure Period.

Similarly, total puff volume initially increased from baseline in the THS 2.2 Menthol arm reaching its maximum on Day 4. This was mainly driven by an increase of average puff volume and the total number of puffs. The total puff volume subsequently decreased during the Ambulatory Period in the THS 2.2 Menthol arm; however, a similar decrease was observed in the mCC arm, resulting in a consistent difference in total puff volume from Day 4 to Day 90 between the THS 2.2 Menthol and mCC study arms.

The initial increase in product use, partially sustained through the Ambulatory Period, together with the immediate increase in total puff volume, were most likely the result of an adaptation process engaged by users to achieve the levels of nicotine desired when switching to a new product which has different characteristics and a lower nicotine yield to that of the own preferred mCC. This finding was consistent with other results as subjective effects and product evaluation showed THS 2.2 Menthol was satisfactory to users, relieved urge-to-smoke and withdrawal symptoms comparably to mCC, and was therefore a suitable replacement for mCC shortly after the first days of use.

Initial changes in some CREs, which are relevant to disease pathways of smoking-related diseases, towards the direction of smoking abstinence suggest that the exposure reduction achieved with switching to THS 2.2 Menthol may translate into reduced risk of smoking-related diseases. However, a longer study period with an increased sample size is required to better determine these outcomes.

There were no SAEs reported by any randomized subject in this study and no randomized subjects were discontinued due to an AE. The majority of AEs were mild in severity; although 12 severe AEs were reported during the Ambulatory Period, all of which were due to abnormal clinical laboratory findings and were unrelated to IP use. The incidence of subjects experiencing AEs during the study was comparable between study arms; however, the frequency of AEs was higher in the THS 2.2 Menthol arm than the mCC and SA arms. As expected, the number of AEs and the percentage of subjects reporting AEs were higher in the Ambulatory Period.

Overall, the study results demonstrated sustained exposure reduction to HPHCs after switching to THS 2.2 Menthol, including in an ambulatory setting; and led to favorable changes in some CREs, while providing an acceptable alternative to users with regards to subjective experience; therefore, THS 2.2 Menthol might be a suitable substitute to mCC for adult smokers, with the potential to reduce the risk of developing smoking-related diseases 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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Not applicable.

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## **15.4 Statistical Output**

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Not applicable.





## 15.4.2 Product Use

Not applicable.

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- [Listing 15.4.4.25.1](#) Analysis of Risk Markers – PP Set
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- [Listing 15.4.4.34](#) Analysis of Biomarkers of Exposure in 4-hour Fraction versus mCC and SA on Day 90 Visit – PP Set
- [Listing 15.4.4.53.1](#) Analysis of QSU-brief Factors and Total Scores – PP Set
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## 16 APPENDICES

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#### 16.1.1 Protocol, Protocol Amendment, and Notes to File

- 16.1.1.1 Study Protocol
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- 16.1.1.3 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
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- 16.1.3.10 IRB Subject Information and Informed Consent Form Version 001 Submission Letter (English)
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- 16.1.4.1 Site 1
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Not applicable.

#### 16.1.6 Randomization Scheme and Codes

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- 16.1.6.2 Biostatistical Addendum to (b) (4)

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- 16.1.9.1 Standardization and Laboratory Reference Ranges
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#### 16.1.10 Publications Based on the Clinical Study



**16.1.11 All Publications Referenced in the Report**

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16.2.1 Case Report Forms For Serious Adverse Events: Subject Number 119

16.2.2 Case Report Forms For Deaths

16.2.3 Withdrawals for Adverse Events

**16.3 CRFs of All Study Participants**

16.3.1 Screen Failures

16.3.2 Enrolled and Not Randomized

16.3.3 Randomized

**16.4 Individual Subjects Data Listings (US Archival Listings)**

Not applicable.